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ACTA OPHTHALMOLOGICA VOL. 55 1977

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A SIMPLE APPARATUS FOR CONTROLLED RATE CORNEAL FREEZING

BY

STEFFEN SPERLING

The construction and operation of an apparatus for controlled rate corneal freezing is described. The cooling is obtained by close thermal contact between a vial holding the cornea and a metal core. A predetermined cooling rate is achieved by partial immersion of the core in a fixed amount of liquid nitrogen. In a preliminary series $\geq 95\%$ endothelial survival was obtained.

Key words: cornea – endothelium – transplantation – freezing rate – dimethylsulfoxide – freezing.

The rapid post mortem deterioration of corneal tissue leaves little room for selection of donor material for penetrating keratoplasty with regard to antigenic properties or endothelial quality. Potential donor material must be used when available or it is wasted. Long term storage of deep frozen corneal tissue would allow the establishment of a bank from which tissue of any desired property could be obtained when needed.

Corneal freezing

In this study and in earlier studies on other aspects of corneal deep freezing attention has been focused on the endothelial cells. This is because a viable

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coherent endothelial layer is the most important factor for the survival of a penetrating corneal graft (Stocker et al 1958)

In an earlier investigation (Sperling 1974) a 90% survival of bovine endothelial cells was achieved after freezing to −196°C Excised corneas were frozen in 8% of the cryoprotective dimethylsulfoxide (DMSO) in human serum The cornea was transferred through [illegible] 4 6 and 8% DMSO in serum at 10 min intervals and frozen in 1 ml of 8% DMSO in a polyethylene vial measuring 20×26 mm After freezing to −196°C in a Linde BF 3 biological freezer the cornea was thawed and endothelial injury was evaluated lightmicroscopically by an increased cellular permeability to Trypane blue The relation between freezing rates and endothelial survival was studied by the freezing of 54 bovine corneas Increased cellular damage was found when the rising part of the freezing curve after the initial crystallization lasted either less than 30 seconds or more than 120 seconds and when the interval −20 to −40°C was passed in less than 4 min In other temperature intervals the rate of cooling could be varied within wide ranges without influence upon the endothelial survival A critical period appearing immediately after onset of crystallisation was also found by Capella et al (1965) and by Mueller (1968)

When the temperature of a mixture of DMSO and serum is lowered by 2–5°C/min the freezing point will often be passed by 2–4°C before the onset of crystallization Once initiated the formation of ice will proceed until the amount of heat liberated by crystallization has raised the temperature to the the freezing point When heat is continuously removed more ice is formed and the freezing point is gradually depressed by the progressive concentration of solutes in the remaining water While the temperature of one g of water is *lowered about 1°C by removal of 1 cal of heat 80 calories must be removed* during transformation of 1 g of water to ice In order to keep the corneal tissue within the observed critical cooling rates the heat removal must be greatly increased while ice is formed as compared with the rate of heat removal before and after this period

Mueller (1968) used a freezer in which the temperature of the cooling bath was regulated by the amount of precooled methanol injected into the bath Controlled rate freezers from Linde Inc operating on a principle of intermittent inlets of liquid nitrogen on a fan in the freezing chamber have been used by Capella et al (1965) and by Sperling (1974) Pakarinen (1969) constructed a freezer in which a flow of cold nitrogen vapour reaching the freezing chamber was regulated by hand Capella et al (1965) have constructed a cornea freezer operating on a slightly different principle in which onset of crystallisation of a cryoprotective solution in a reference vial initiates an electric fan speeding up the rate of evaporation from a nitrogen compartment (Polack 1971) In this paper the construction and the operation of an apparatus for controlled rate freezing of human corneas is described

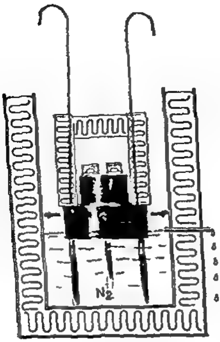

Fig 1
Composite picture of a section through the freezing apparatus

Method and Material

The construction of the freezing apparatus is shown in Fig 1 The apparatus consists of an iron core an insulation cap and a liquid nitrogen compartment The core is kept at a set distance from the bottom of the nitrogen compartment by three 8 mm bolts Thermal contact between the bolts and the core is achieved by greasing the connections with heat conducting paste (Danfoss type /41E, 0110) The nitrogen compartment is made of an inner PVC sheet surrounded by expanded polyurethane The nitrogen level is controlled by an overflow bore

When the apparatus is placed in liquid nitrogen the temperature of the core will drop as heat is removed from the metal The rate of heat removal from the vial is directly proportional to the temperature difference between vial and core and related inversely to the insulation of the vial The insulation power of the bottom of the vial is low Consequently small alterations in the temperature difference between vial and core will have a large influence upon the rate of heat removal from the vial When the cryoprotective solution crystallizes the temperature in the vial will stay at the freezing point while the temperature drop of the core will be practically unaffected by the small amount of heat released from the vial The close thermal contact between vial and core will ensure the proper increase in the rate of heat removal from the vial

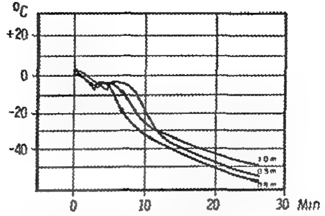

Fig 2
Redrawing of single freezing curves obtained in separate runs from the centre of 14 x [illegible] mm polyethylene vials holding 0 6 ml 0 8 ml and 1 0 ml of 8 % DMSO in human serum

In this apparatus the *only* variable parameters influencing the corneal freezing rate will be the amount of fluid in the vial the freezing point of the fluid and the degree of undercooling before onset of crystallization The curves redrawn in Fig 2 illustrate how the construction of this apparatus tends to minimize the effect of volume differences and the differences in the temperature reached before crystallization on the rate of cooling in the vial It is also seen from Fig 2 that freezing rates produced by this apparatus lie within the limits which have previously been found to be critical for bovine endothelial cells (Sperling 1974) The cooling rate of the apparatus will be directly proportional to the facility of heat removal from the metal core and related inversely to the amount of heat contained in the core The apparatus was calibrated stepwise in a series of freezing experiments in which a thermocouple was placed in cryoprotective solution After each of nine runs the freezing rate was increased by cutting a slice of the top of the core

Before freezing corneal tissue was transferred through 2 4 6 and 8 % DMSO at 10 min intervals DMSO was dissolved in human serum type A Rh pos or in 0 % albumin (Kabi) The tissue was frozen in 8 % DMSO in serum in polyethylene vials measuring 14 x 10 mm with a bottom thickness of 0 3 mm The vial containing the cornea in 8 % DMSO *was placed on top* of the iron core on a layer of heat conducting paste The insulation cap was placed over the top of the core and the core was lowered into the nitrogen compartment When the temperature in a reference vial on the core reached –70 C the entire freezing apparatus was transferred to –1 0°C in a liquid nitrogen storage tank

When the temperature in the reference vial had reached –160°C the apparatus was removed from the liquid nitrogen tank and the cornea was thawed by partial immersion of the vials in water at 60°C. After a brief rinsing in 0 9 % NaCl the cornea was stained with 0 25 % Trypane blue for 1 min (Sperling 1974) and radial incisions were made The cornea was placed on a microscope slide covered by a floating cover glass and studied under an ordinary Zeiss laboratory microscope

10 human corneas with a rim of 1⅓ mm of scleral tissue were obtained from cadaver eyes in situ A human cornea will maintain its original shape when supported by a narrow rim of sclera A partial scleral section was made with the 13 mm trephine after careful centering through the trephine body The final section of sclera was made with a pair of curved scissors over the intact choroid The cornea was separated from the bulbus by gentle traction applied to the scleral rim and sectioning of the trabeculum by a 6–8 mm strip of razor band in a needle holder Excised corneas were placed on agar plates resting on the scleral rim and transported to the laboratory In experiments with human corneas the entire cornea with the scleral rim was used

Preliminary Results

A small study was carried out on 10 human corneas Each cornea was frozen in 1 ml of cryoprotective fluid containing 8 % DMSO Corneas were thawed in water at 60 C transferred to serum at room temperature and left for 10 min before staining The treatment of the corneas before freezing the composition of the cryoprotective fluid the temperature of equilibration and the endothelial survival is indicated in Table I $\leq$ 5 % of stained endothelial cells were found when DMSO was dissolved in serum and when it was dissolved in 20 % albumine and 10 % saccharose (Expts 1 2) $\leq$ 5 % stained cells were found after equilibration at 4°C and at 22°C (Expts 1 2 and 7 8) $\leq$ 5 % stained cells were also found in a cornea left at 4°C resting on the scleral rim for 18 h (Expt 5) and in one cornea left in the cadaver at room temperature for 18 h (Expt 6) After freezing areas showing 50–90 % of stained cells were found in one cornea which had been folded in the central area by resting on the epithelial side for 18 h at 4 C in moist chamber (Expt 5) and in one cornea in which the endothelium had been in contact with iris during the excision from the globe (Expt 3) The corneal shape and texture appeared unaltered after thawing but the thickness was reduced

Comments

In an earlier study on the freezing of bovine corneas a maximum of 90 % surviving endothelial cells was obtained in a Linde BF 3 freezer (Sperling 1974)

When the cryoprotective solution is undercooled the initial formation of ice crystals may start anywhere in the vial As ice has a larger thermal capacity than the cryoprotective solution the ice crystals will have a tendency to

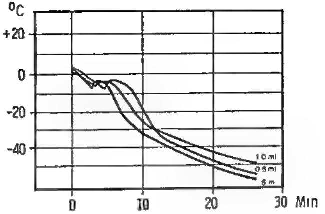

Fig 2

Redrawing of single freezing curves obtained in separate runs from the centre of 14 × 12 mm polyethylene vials holding 0 6 ml 0 8 ml and 1 0 ml of 8 % DMSO in human serum

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grow as a coherent front in contact with areas from which heat is removed Solutes will be concentrated between the growing ice crystals and ahead of the ice front The heat transference properties of the vial and the cooling method applied will determine the shape and the progression of the ice front Identical cooling rates will give rise to differences in alteration of solute concentration when heat is removed from the bottom of the vial in the apparatus used in this study and when heat is removed from the sides of the vial in the Linde freezer In the apparatus used in this study the alteration of solute concentration during crystallization will be different at different levels measured from the bottom of the vial Despite these theoretical differences more than 95 % of the human endothelial cells survived deep freezing in this study

In an experimental freezer it should be possible to vary the freezing rate within wide ranges The demands on a freezer for routine work are different exact reproduction of a single freezing curve simplicity of operation and a construction which reduces the possibilities of human and mechanical errors to a minimum now being of prime importance The total absence of mechanical and electrical components in the freezer here described makes this freezing apparatus suited for routine freezing of corneal tissue The results of the pilot study of the freezing of human corneas indicate that high survival rates can be obtained after freezing in this apparatus A study of human corneas frozen in a light weight apparatus operating on the same principles as the apparatus described in this paper are in progress

References

Capella J A Kaufman H E & Robbins J E (1965) Preservation of viable corneal tissue *Arch Ophthal (Chicago) 74* 669–673

Dohlman C H & Anseth A (1957) The swelling pressure of the ox corneal stroma *Acta ophthal (Kbh) 35* 73–84

Ehlers N (1966) Variations in hydration properties of the cornea *Acta ophthal (Kbh) 44* 461–471

Mueller F O (1968) Experiments on canine corneal donor material stored in liquid nitrogen *Brit J Ophthal 52* 649–653

Pau H (1953) Beitrag zur Physiologie und Pathologie der Hornhaut *Graefes Arch Ophthal 154* 579–607

Pakarinen P (1969) Preservation of the cornea for penetrating keratoplasty An experimental study *Acta ophthal (Kbh) Suppl 106*

Polack F M (1971) Cryopreservation of corneas for penetrating keratoplasty *Amer J Ophthal 71* 505–515

Sperling S (1974) Corneal cryopreservation evaluated by Trypane blue staining *Ophthal Res 6* 23–35

Sperling S (1976) Toxicity of DMSO to bovine corneal endothelium *Ophthal Res 8* 233–240
Stocker F W Eiring A Georgiade R & Georgiade N (1958) Evaluation of viability of donor tissue for corneal grafting *Trans Amer Ophthal Soc 1958* 217–238

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ASEPTIC THROMBOSIS OF ORBITAL VEINS AND CAVERNOUS SINUS

Clinical Symptomatology

BY

GUDRUN BRISMAR and JAN BRISMAR

Occlusion or thrombosis of the superior ophthalmic vein or of the cavernous sinus is an unspecific finding that may be secondary to different disorders such as tumours of the skull base or nasopharynx Some times however no underlying disorder is found in spite of an extensive clinical and radiological evaluation Eight such cases are here presented Similar cases have previously been described both as examples of the Tolosa Hunt syndrome and as aseptic cavernous sinus thrombosis The literature on these two disorders is reviewed and different diagnostic criteria discussed

Key words aseptic cavernous sinus thrombosis – cavernous sinus pathology – orbit pathology – orbit phlebography – orbit venous thrombosis – superior orbital fissure syndrome – Tolosa Hunt syndrome

The oculo motor nerves and the ophthalmic division of the trigeminal nerve are located close together at the cavernous sinus and together with the superior ophthalmic vein pass through the superior orbital fissure The optic nerve and the ophthalmic artery reach the orbit through the optic canal Disorders affecting the anterior part of the cavernous sinus or the superior orbital fissure will cause identical symptoms and signs affection of the 3rd 4th and 6th cranial

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nerves the ophthalmic division of the trigeminal nerve as well as impairment of the venous drainage of the orbit If the disease process extends further back the maxillary and mandibulary divisions of the trigeminal nerve may also be involved The optic nerve will not be affected as long as the disorder remains limited to the superior orbital fissure or the cavernous sinus

Retro orbital pain accompanied by ophthalmoplegia may be caused by a variety of disorders aneurysms of the internal carotid artery carotid cavernous fistulas neoplasms and inflammations (including specific inflammations such as tuberculosis or syphilis) of the cavernous sinus or in the area of the superior orbital fissure (Godtfredsen 1964)

In 1954 Tolosa presented his classic case of a superior orbital fissure syndrome proven at autopsy to be caused by granulomatous changes in the cavernous sinus wrapping the intracavernous portion of the internal carotid artery Hunt et al (1961) presented 6 cases with retro orbital pain and involvement of the oculo motor nerves steroid treatment was employed in 5 cases and was in all cases followed by prompt regression of symptoms and signs This syndrome is now known as the Tolosa Hunt syndrome and is believed to be caused by a low grade non specific inflammation of the cavernous sinus – superior orbital fissure region Several cases with this syndrome have since been presented by different authors (Table II) The diagnostic criteria in all these materials have been the clinical symptomatology – in most materials a prompt answer to steroid treatment has also been requested In a few cases (Lakke 1962 Levy et al 1975 Schatz & Farmer 1972) histological examinations have been per formed confirming Tolosa s findings of granulomatous tissue in the cavernous region

Septic cavernous sinus thrombosis is not a difficult differential diagnosis in the evaluation of a superior orbital fissure syndrome It is a fulminant disease that in addition to ophthalmological symptoms also presents with alarming general symptoms such as septic temperature headache nausea vomiting giddiness and somnolence Aseptic thrombosis of the cavernous sinus has been considered extremely rare (Walsh & Hoyt 1969) Rad et al (1971) however described 10 cases of aseptic thrombosis of the cavernous sinus all presenting as superior orbital fissure syndromes and 9 of them verified by phlebography Heparin therapy was tried and followed by improvement in 8 cases These authors concluded that several of the previously presented Tolosa Hunt cases may in fact have suffered from a thrombosis of the cavernous sinus

The aim of the present report is to present 8 new cases with an unexplained occlusion or defective filling of either the superior ophthalmic vein or the cavernous sinus and to discuss possible differential diagnoses in the light of the previous literature

Material and Methods

In 7 patients out of a phlebographic material of 200 examinations no explanation could be found for an occlusion or defective filling of the superior ophthalmic vein or of the cavernous sinus in spite of extensive clinical and radiological investigations (see Brismar & Brismar 1976b for details) An additional case fulfilling the same criteria was kindly submitted by Drs C Daunius and H Munthe Vänersborg Trollhattans Centrallasarett Sweden The material consists of 5 women and 3 men 45–73 years of age The clinical records of these patients have been scrutinized and the symptoms and signs analyzed The phlebographic findings have been presented in detail in a previous report (Brismar & Brismar 1976b) in which the patients were designated the same numbers Case 8 has been presented from radiological viewpoints in a separate article on skull base phlebography (Brismar et al 1976)

Results and Comments

The results are summarized in Table I Five of the patients (cases 2 4–7) had similar case histories (two of which are presented below) with unilateral (cases 2 4 5) or bilateral (cases 6 7) affection of the eye muscle nerves and retro orbital pain The onset of ophthalmological symptoms and signs was rapid in all 5 patients in one of them (case 7) however preceded by a month of headache Vision was affected to some degree in four of the patients in this group (all except case 5) an unequivocal affection of the optic nerve was found in 3 patients (cases 4 6 7) who exhibited marked decrease of visual acuity defective colour vision (cases 4 6) and visual field defects (cases 6 7) in spite of normal fundoscopic findings A spontaneous improvement occurred in all five cases but in three cases (cases 2 6 7) recurrences took place In two cases (cases 2 4) a history of a previous episode was obtained All the recurrences had an acute onset Steroid treatment was tried in only one of the patients in this group (case 6) but had no effect on the first attack In association with the recurrences in this patient, when she presented with signs of optic nerve affection the effect of steroid treatment was good I O P (applanation tonometry) was normal in all these cases

Case 4 A 58 year old previously healthy man had 4 years prior to admission exhibited a left trochlear nerve palsy that spontaneously disappeared in the course of a few days Eight days prior to admission he noted onset of diplopia followed 2 days

Table I

Symptoms and signs in 8 patients with unexplained defect filling of the superior ophthalmic vein or the cavernous sinus (right sided findings presented above left sided)

Pat. No	Sex age	Type of onset	Initial symptom	Orbital pains	Cranial nerve involvement
1	F 63	Insidious	Lid puffiness	0 0	0 0
2	F 56	Acute	Diplopia	+ 0	III IV VI V_1 0
3	F 63	Acute	Bubble in ear diplopia headache	0 +	0 III IV VI $V_{1,2}$ VII
4	M 58	Acute	Diplopia	0 ++	0 III IV VI
5	M 72	Acute	Pains nausea	0 +++	0 III IV VI
6	F 53	Acute	Nausea headache diplopia	+ 0	VI VI
7	M 72	Insidious	Headache for 2 months then diplopia	+ +1)	III VI VI?1)
8	F 44	Insidious	Headache, diplopia	+1)	III1) IV1) VI1) $V_1$1) III IV VI $V_1$1) V1)

later by constant pain in the left eye and a left sided ptosis and 5 days later also by subjectively decreased vision in the left eye nausea and vomiting Ophthalmological examination on admission revealed on the left side visual acuity 0.[illegible] defective colour vision 3 mm relative proptosis affection of NIII NIV and NVI and an abnormally slow pupillary reaction to light Fundoscopy revealed slight nasal disc oedema 1–2 D disc protrusion and slight venous dilatation Normal findings on the right side Orbital phlebography and left sided carotid angiography demonstrated an occlusion of the posterior part of the left superior ophthalmic vein Skeletal films of the skull and orbits radionucleide brain scan and pneumoencephalography were normal Nasopharyngoscopy was normal The symptoms and signs completely and spontaneously disappeared in the course of one month and had not recurred [illegible] weeks later The patient has not appeared since

Pupil involv	Proptosis	Lid swelling	Conjunct venous dilat	Retinal venous dilat	Disc blurring
Miosis	0	+	0	0	0
Miosis	4 mm	+	?	0	0
0	3 mm	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
R > L	0	0	0	+	0
	3 mm	0	0	+	1–2 D
0	0	0	0	0	0
0	5 mm	0	+	0	0
0	0	0	0	0	0
0	0	0	0	0	0
R > L[1)]	0	0	+	0	0
	0	0	0	0	0
0	2 mm[1)]	0	0	0	0
0	0	0	0	+	2 D

(cont next pages)

Case [illegible] A 53 year old woman with severe coxarthrosis one evening experienced nausea headache and diplopia (caused by a right abducent nerve palsy) Nineteen days later a left abducent nerve palsy followed No other pathological findings were present at admission except for a left sided refraction amblyopia Orbital phlebo graphy demonstrated defective filling of both cavernous sinuses and of the posterior part of the right superior ophthalmic vein Skeletal films of the orbits and skull base (including tomography) bilateral carotid angiography pneumoencephalography as well as nasopharyngoscopy with biopsies were negative. Steroid treatment (Predni solone 15 mg × 3) was initiated but had no effect and was withdrawn after 3 weeks Three months later when the abducent nerve palsies had improved somewhat the vision in the right eye rapidly became impaired the visual acuity decreased to 0 3 the colour vision became defective and a small paracentral scotoma developed A

Table 1 (cont.)

Pat No	Sex age	Visual acuity max – min	Colour vision)	Visual fields[3)]
1	F	0 6	–	Bjerrum scotoma
	63	0 7	–	0
2	F	1 0 – 0 7	–	0
	56	1 0	–	0
3	F	0 9	–	0
	63	0 6	–	0
4	M	1 0	18/18	0
	58	1 0 – 0 7	1/18	0
5	M	1 0 – 0 9	–	0
	72	1 0	–	0
6	F	1 0 – 0 1[1)]	0/18[1)]	scotoma[1)]
	53	0 7 (ambl)	18/18	0
7	M	1 0 – 0 1	–	temp defect
	72	1 0	–	0
8	F	1 0	18/18	0
	44	1 0 – 0 4[1)]	0 18	central scotoma[1)]

Notes [1)] symptom or sign not present in actual attack) A m Bostrom Kugelberg

repeat orbital phlebogram demonstrated bilaterally improved filling of the cavernous sinuses Prednisolone therapy was again initiated and was in a day followed by improvement of the visual acuity Two months later the visual acuity in the right eye was normal and the colour vision only slightly defective Another month later the visual acuity in the right eye again rapidly decreased this time to 0 1 and once more rapidly normalized following steroid treatment A more pronounced defect in the colour vision remained however as did slight bilateral abducent nerve palsies The patient has not returned for consultation in the following ? years

One additional patient (case 5) presented with symptoms similar to those of the group presented above but differing in some respects The onset of symptoms and signs was for a few days accompanied by a bubbling sensation in the ipsilateral ear

Therapy effect	Spont healing actual attack	Follow up time[4])	Number of recurrences	Comments
[illegible]	[illegible]	7.5 years	0	Glaucoma simplex since 1964
0	4 months	5 years	2 previous	Residual damage slight ptosis and vertigo
steroids 0 eff	[illegible] months	15 months	0	Chronic rheumatoid arthritis pyelonephritis Only residual damage NVII
[illegible]	1 month	4 years	1 previous	No residual damage.
0	6 weeks	22 months	0	No residual damage Later retinal break in left eye
steroids 0 effect on 1st episode	5 months	8 months	2 later	Slight residual bilateral NVI palsies
0	[illegible] months	15 months	1 later	No residual damage
steroids good effect in few days	–	4 5 years	1 previous 3 later	Progressive course → exitus

[5]) Goldmann perimetry [4]) from onset of first attack

In addition to the eye muscle nerve palsies the patient also had a facial nerve palsy indicating a more extensive lesion I O P was normal The symptoms and signs did not respond to steroid treatment but spontaneously decreased and have not since (15 months) recurred Though it cannot be excluded that this patient belongs to the group presented above it is also possible that she constitutes an example of a thrombotized spontaneous carotid cavernous fistula (Brismar & Brismar 1976a)

Another patient (case 8) originally behaved as the patients in the main group The disorder however had a more aggressive and progressive course with ultimate extensive involvement of the intracranial arteries and terminated in death five years later Steroid treatment in this case initially had some effect

The last patient (case 1) differs in most respects from the remaining material

Case 1 This 63 year old woman had in early childhood suffered from phlyctenular keratoconjunctivitis healing with bilateral corneal scars For 8 years she had been having treatment for bilateral glaucoma simplex Two years prior to admission a left sided proptosis was noticed as was a palpebral oedema (which could possibly have been present for several years) Ophthalmological examination was otherwise normal

Orbital phlebography demonstrated an occlusion of the posterior part of the superior ophthalmic vein on the left side with collaterals bypassing the occlusion The patient has since been followed for 4 years and has undergone a trabeculectomy operation in the right eye because of unsatisfactory regulation of the intraocular pressure. The findings have otherwise remained the same with 2-3 mm left sided proptosis and slight lid puffiness around both eyes

This patient was the only one in the material without any pains and was also the only one without any involvement of cranial nerves In all the other patients spontaneous remissions or healing were seen but in this patient the findings have remained unchanged Though it cannot be entirely excluded that this patient represents an end stage of the same disorder as the main group presented above it is more likely that she suffers from some other disorder such as fibrotized orbital pseudotumour

Discussion

Considering the criteria that were used to select this material (defective filling or occlusion of the superior ophthalmic vein or of the cavernous sinus unexplained in spite of detailed evaluation) and realizing that the patients were subjected to phlebography as possible orbital tumours the homogeneity of the material is remarkable Only one patient (case 1) clearly differs from the others with respect to case history and symptomatology

Nine out of the 10 patients in the material of Rad et coll (Rad et al 1970 Rad 1971 Tornow 1971) were subjected to orbital phlebography and exhibited findings similar to those of our material The symptoms and signs in their material (concluded in Fig 1) essentially consisted of retro orbital pains eye muscle palsies and conjunctival and retinal venous congestion These findings led the authors to establish the diagnosis of aseptic cavernous sinus thrombosis Eight of the patients were then treated with heparin 2 in combination with penicillin all with good results Steroid treatment was not used in any of the cases

The same findings at orbital phlebography have been encountered in 3 patients by Sondheimer & Knapp (1970) and in one each by Milstein & Morretin (1971) and Hunt (1976) These patients were however selected by the diagnostic criteria suggested by Hunt et al (1961) and again emphasized by Hunt (1976) (1) retro orbital pains (2) involvement of structures related to the anterior

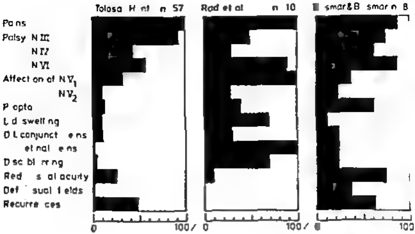

Fig 1

Incidence of various symptoms and signs in the concluded Tolosa Hunt materials a material of aseptic cavernous sinus thrombosis and the present material

cavernous sinus and the superior orbital fissure (3) exhaustive studies to disclose underlying disorder are negative (4) exquisite sensitivity to steroids Hunt also mentioned that symptoms may last for days or weeks that spontaneous remissions occur and that the attacks may recur Cases previously published as Tolosa Hunt syndrome are listed in Table II All these patients have been selected according to symptoms and signs steroid treatment has been employed in the majority of cases and when used has always been followed by a prompt regression of symptomatology As expected from the principles of selection the symptoms and signs are similar in the different Tolosa Hunt materials and they are therefore summarized in Fig 1 to permit a comparison with our material and the material of Rad et coll Pains and cranial nerve involvement are dominating features in all three materials Signs of venous congestion are prominent in the material of Rad et coll quite frequent in our material and rare in the Tolosa Hunt material Decreased vision is seen in a large proportion of our cases not infrequently in the Tolosa Hunt material and also exists in the material of Rad et coll Recurrences are frequently seen in both our material and the Tolosa Hunt material but are not described in the material of Rad et coll However the follow up period in the latter material is short for several of the patients

The Tolosa Hunt syndrome and the aseptic cavernous sinus thrombosis

Table II

Symptoms and signs in different Tolosa Hunt materials (I–XI) and in a material of aseptic cavernous sinus thrombosis (XII)

Material number	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	Σ	XII
n	1	6	1	5	1	22	1	4	3	1	12	57	10
Females/males	0/1	4/2	0/1	2/3	0/1	7/15	1/0	4/0	1/2	0/1	8/4	27/30	4/6
Age range	47	9–57	47	57–75	36	10–69	15	39–61	43–60	43	24–75	9–75	21–64
Pains	1	6	1	5	1	22	1	4	3	1	12	57	10
Affection NIII	1	6	1	4	1	20	1	3	3	1	12	53	5
NIV	1	4	1	2	1	9	1	2	1	0	3	[illegible]	3
NVI	1	4	1	4	1	9	1	3	3	0	6	33	9
NV_1	1	3	1	2	0	6	–	3	1	0	2[1]	19[1]	10
NV_2	0	–	0	1	0	0	–	3	2	0	1[1]	7[1]	3
NV_3	0	–	0	0	0	0	–	1	1	0	0[1]	2[1]	0
Involvement of pupil	–	1[1]	0	3	1	13	0	4	1	0	7[1]	30[1]	[illegible]
Proptosis		1[1]	1	1	1	0[3]	1	2	–	1	–	3[1]	4
Lid puffiness	–	–	–	1	0	5[3]	–	–	–	–	–	6[1]	7

Dil conjunctival veins	–	0[1]	–	1	0	5[3]	0	–	–	–	–	6[1]	3
Dil retinal veins	0	0[1]	0	0	0	0	0	0	0	1	–	1[1]	10
Disc blurring	0	0[1]	0	0	1	0	0	0	0	1	–	2[1]	7
Reduced visual acuity	1	3	1	0	1	3	1	?	0[1]	1	1	14[1]	1
Defect visual fields	0	–	0	0	0	–	0	1	0	0	–	1[1]	–
n with recurrences	1	5	1	3	1	7	0	2	2	1	5	28	0
n steroid treated/n improved	0/0	5/5	0/0	5/5	1/1	13/13	1/1	3/3	3/3	1/1	12/12	44/44	0
n heparin treated/n improved	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	8/8
n non treated/n improved	0/0[5]	1/1	1/1	0/0	0/0	9/7	0/0	0/0[5]	0/0	0/0	0/0	11/9	2/1

Materials I = Tolosa (1954) II = Hunt et al (1961) III = Lakke (1962) IV = Smith & Taxdal (1966) V = Other (1967) VI = Mathew & Chandy (1970) VII = Milstein & Morretin (1971) VIII = Schatz & Farmer (1972) IX = Sondheimer & Knapp (1973) X = Hallpike (1973) XI = Hunt (1976) Σ = Materials I–XI (all Tolosa Hunt materials) concluded XII = Rad et al (1971)

Notes – Not specified [1] Information not available on all patients [2] Age only given in decades [3] 5 patients showed varying combinations of conjunctival oedema congestion of the conjunctiva and minimal prominence of the eye [4] in most of our cases [5] One patient died following surgery

may evidently present with the same symptoms and signs and also give the same phlebographic findings The response to therapy thus constitutes the most important differential diagnostic criterion the Tolosa Hunt cases respond dramatically to steroid treatment the thromboses improve on heparin therapy The value of this criterion is nevertheless decreased by the fact that nobody knows the effect of steroid treatment in cases with aseptic cavernous sinus thrombosis neither has heparin therapy been tried on Tolosa Hunt patients The use of the response to therapy as a diagnostic criterion is further complicated by the fact that both the aseptic cavernous sinus thrombosis (Rad et al 1971) and the Tolosa Hunt syndrome (Hunt 1976) have a tendency to spontaneous remission Thus without denying the fact that both the Tolosa Hunt syndrome (as verified by surgery and by autopsy) and the aseptic cavernous *sinus thrombosis exist as diagnostic entities it should be emphasized that in* a large number of cases the results of clinical and radiological examinations do not permit a valid differentiation between these two diagnoses That is also *true for our material In only 2 of our cases (cases 5 6) did the phlebographic* findings (unilateral and bilateral filling defects in the cavernous sinus respectively) suggest the presence of a thrombosis – in the remaining cases no differentiation between Tolosa Hunt syndrome and aseptic cavernous sinus thrombosis could be made

It must further be emphasized that the clinical course of the disease and its response to steroid therapy are not only invalid criteria in the differentiation between the Tolosa Hunt syndrome" and an aseptic cavernous sinus thrombosis but sometimes also fail to differentiate between these two disorders and more serious ones Thomas & Yoss (1970) presented a material of 109 patients with an intracranial parasellar lesion with involvement of two or more parasellary situated cranial nerves A breakdown of their material into disease categories gave 70 neoplasms 19 aneurysms and 13 inflammations (of those 3 Tolosa Hunt cases) About half the cases (regardless of to which category they belonged) had a rapid onset of symptoms One fifth of the cases showed spontaneous remissions 12 neoplasms 7 aneurysms and 2 inflammations Two of their patients that later proved to have parasellar neoplasms (one chordoma and *one giant cell tumour) demonstrated remissions following systemic steroid* treatment – in one case the remission lasted 4 years The authors concluded Etiological conclusions should not be drawn from the patients response to steroid therapy since both inflammatory and non inflammatory lesions are potentially capable of responding to such treatment" We cmpletely agree with that statement and also wish to add that the response to heparin therapy is likewise not a valid diagnostic test

Conclusion

Both the Tolosa Hunt syndrome and the aseptic cavernous sinus thrombosis exist as diagnostic entities They may however present with similar symptoms and signs and may appear identical on phlebography

The response to steroid or heparin therapy is not a valid criterion in the differential diagnosis between these two disorders and in many cases a differentiation is impossible

Neither the clinical symptoms and signs the course of the disease and the phlebographic findings nor a positive response to steroid or heparin therapy can exclude a more serious underlying disorder Such a disorder must always be excluded by an extensive clinical and radiological evaluation that should include carotid angiography tomography of the skull base and nasopharyngoscopy with blind biopsies

Orbital phlebography has a definite value in the diagnosis of these patients by objectively verifying the lesion in the cases with Tolosa Hunt syndrome or with an aseptic cavernous sinus thrombosis In some cases it also permits a differentiation between these two disorders

References

Brismar G & Brismar J (1976a) Spontaneous carotid cavernous fistulas Phlebographic appearance and relation to thrombosis *Acta radiol (Diagn) (Stockh) 17* 180–192

Brismar G & Brismar J (1976b) Thrombosis of intraorbital veins and cavernous sinus *Acta radiol (Diagn) (Stockh)* in press

Brismar G Brismar J & Cronqvist S (1976) Complications of orbital and skull base phlebography *Acta radiol (Diagn) (Stockh) 17* 274 280

Godtfredsen E (1964) Studies on the cavernous sinus syndrome 1 Incidence aetiology and differential diagnosis of infranuclear ophthalmoplegias *Acta neurol scand 40* 69–75

Hallpike J F (1973) Superior orbital fissure syndrome Some clinical and radiological observations *J Neurol Neurosurg Psychiat 36* 486–490

Hunt W E (1976) Tolosa Hunt syndrome one case of painful ophthalmoplegia *J Neurosurg 44* 544–549

Hunt W E Meagher J N LeFever H E & Zeman W (1961) Painful ophthalmoplegia Its relation to indolent inflammation of the cavernous sinus *Neurology (Minneap) 11* 56–62

Lakke J P (1962) Superior orbital fissure syndrome Report of a case caused by local pachymeningitis *Arch Neurol (Chic) 7* 289–300

Levy I S Wright J E & Lloyd G A S (1975) Orbital and retroorbital pseudotumours *Mod Probl Ophthal 14* 364–367

Mathew N T & Chandy J (1970) Painful ophthalmoplegia *J neurol Sci 11* 243–256

Milstein B A & Morretin L B (1971) Report of a case of sphenoid fissure syndrome studied by orbital venography *Amer J Ophthal 72* 600–603

Other A (1967) Painful ophthalmoplegia Report of a case *Acta ophthal (Kbh) 45* 371–373

Rad M v (1971) Das klinische Bild der blanden Sinus cavernosus Thrombose und ihre Behandlung *Radiologe 11* 402–404

Rad M v Wolf P & Tornow K (1971) Die blande Thrombose des Sinus cavernosus *Dtsch med Wschr 96* 457–464

Schatz N J & Farmer P (1972) Tolosa Hunt syndrome the pathology of painful ophthalmoplegia In *Symposium of the University of Miami and the Bascom Palmer Eye Institute Neuro ophthalmology* Vol 6 pp 102–112 C V Mosby St Louis

Smith J L & Taxdal D S R (1966) Painful ophthalmoplegia the Tolosa Hunt syndrome *Amer J Ophthal 61* 1466–1472

Sondheimer F K & Knapp J (1973) Angiographic findings in the Tolosa Hunt syndrome painful ophthalmoplegia *Radiology 106* 105–112

Thomas J E & Yoss R E (1970) The parasellar syndrome problems in determining etiology *Mayo Clin Proc 45* 617–623

Tolosa E (1954) Periarteritic lesions of the carotid siphon with the clinical features of a carotid infraclinoidal aneurysm *J Neurol Neurosurg Psychiat 17* 300–302

Tornow K (1971) Beitrag zur angiographischen Diagnostik der blanden Thrombose des Sinus cavernosus *Radiologe 11* 405–409

Walsh F B & Hoyt W F (1969) *Clinical Neuro Ophthalmology* p 1898 3rd ed Williams & Wilkins Co Baltimore

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EFFECTS OF OPHTHALMIC VEHICLES ON THE STABILITY OF THE PRECORNEAL FILM

BY

MOGENS S NORN and ANNA OPAUSZKI

The break up time (B U T) of the precorneal film has been studied before and after application of 34 different vehicles The material examined comprised 646 eyes
Maximum increase of the B U T was obtained with 2 % methyl cellulose (four times) and 10 % polyvinyl alcohol (seven times) These vehicles in the usually employed concentrations fat free ointment (polyethylene glycol) acetyl cysteine and polysaccharide (dextran) affected a less pronounced prolongation
The B U T was reduced four or five times by fatty anhydrous ointments and by silicone oil about two or three times by emulsions and oils and twice by 0 01 % benzalkonium chloride
The clinical significance of the B U T alterations is discussed

Key words ophthalmic vehicles – ointment – oil – artificial tears – precorneal tear film – break up time (B U T) – wetting time – wettability – stability

The stability of the precorneal tear film is an important factor in the integrity of the epithelium Some ophthalmic vehicles add to the stability

We treat an unstable precorneal film (dry eye syndrome) with artificial tears and we rub corresponding substances (wetting agents) upon hard contact lenses

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in order to protect the cornea We add vehicles to eye drops to prolong the period of contact of the active drug in the hope of promoting its absorption

The stated factors (stability of the precorneal film contact period and promoted absorption) may vary independently They are concepts that should definitely be kept apart

Norn in 1969 introduced a clinically useful method for objective measurement of the stability of the precorneal film (wetting time) Lemp et al in 1970 assessed the same method calling it break up time (B U T) The time interval is measured from the conclusion of a blink till occurrence of holes in the pre corneal film

The B U T is independent of the patient s age (Norn 1969 Lemp et al 1973) It tends to be longer in males than in females (Norn 1969 not confirmed by Lemp 1973) In normal eyes the B U T is 10 seconds or longer (Lemp 1973)

Lemp et al (1975a) studied the effect of artificial tears on 12 normal subjects They tested 13 different commercial preparations measuring before and re peatedly (at 15 minute intervals) after the instillation The B U T increased significantly most often two or three times as a sign of improved stability of the precorneal film The effect was most prolonged with those drugs to which B P Polymer had been added (adapt, adapettes adsorbotear) and tears naturale (Alcon 0413) about 90 min against 35–60 min for the others (lacril liquifilm I and II isoptotears contique ultratears presert lytears – though no effect of tearisol) They point out that salt concentration and preservatives may influence the B U T

The preservative benzalkonium chloride in a concentration of 0 01 % reduces the B U T four times in rabbit and about twice in man (Wilson et al 1975 31 human eyes)

The *angle of contact* between precorneal film and dry cornea gives us an indirect impression of the stability of the precorneal film a narrow angle effecting greater extension of fluid and consequently better wettability and film stability

Lemp et al (1975b) developed such a method on enucleated rabbit cornea However the results are not directly transferable to human clinical practice

Rocher (1975) and Shively (1975) measure the angle with a view to contact lenses

The *contact period* and the influence of vehicles on this can be indicated by estimating the reduced outflow to the nose (Linn & Jones 1968) or by measuring the fall of the technetium suspension concentration in the conjunctiva (Patton et al 1975 Hardberger et al 1975)

The dependence of the *absorption* on the vehicle can for instance be mea sured by uptake of radioactive ^{3}H thymidine in the epithelial cells of the rabbit

cornea (Swanson et al 1968) As for neomycin the effect of the vehicle on pseudomonas keratitis has been studied on rabbit by Bach et al 1970

We cannot decide on the basis of the literature whether methyl cellulose (MC) or polyvinyl alcohol (PVA) is preferable as an ophthalmic vehicle The results differ dependent on the parameters examined concentration viscosity etc (cf Krishna et al 1964 1965 Linn & Jones 1968 Swanson et al 1968 Bach et al 1970 Hardberger et al 1975 Patton et al 1975)

Ointment and oil have the opposite effect of MC and PVA They reduce the B U T and consequently the stability of the precorneal film thus tending to damage the epithelium (Norn 1975)

The object of the present study has been to assess on the basis of human experiments the influences of well known and less familiar vehicles on the stability of the precorneal film We have concentrated particularly on investigating the damaging effect of ointments on the precorneal film and whether other harmful vehicles exist further whether MC or PVA is preferable and which substance and concentration prolongs the B U T maximally

Method

The patient was placed at a Haag Streit slit lamp in a half lit room 10 μl of a fluorescein mixture with a local anaesthetic added was instilled This anaesthetic had no influence on the B U T (Norn 1969) The mixture was composed as follows

fluorescein 0 125 %
oxibuprocaine (Novesin®) 0 3 %
phenylmercuric nitrate 0 0025 %
sodium chloride to isotonicity

The patient was requested to blink two or three times A stop watch was started immediately after the conclusion of the final voluntary complete blink. The patient then looked straight forward without blinking The lid was not supported The smooth fluorescent precorneal film was studied in the slit lamp (ten times magnification) The light was a 1–2 mm broad obliquely incident vertical cobalt filtered beam of light which was moved from side to side over the cornea until the first hole was noticed in the precorneal film The stop watch was stopped and the B U T read in seconds

The examination was repeated after renewed blinking

The average of the two examinations constituted the initial B U T

The ophthalmic vehicle to be studied was then instilled using the original dropping bottle (about 50 μl)

One or two min later the fluorescein mixture was instilled again and the B U T was read twice

Statistics

The ratio of the initial B U T average to the B U T after the installation of a vehicle was calculated separately for each case The mean B U T factor concerning each vehicle was calculated with a standard error of the mean (SEM)

The *coefficient of variation* of the two initial B U T determinations was calculated by the formula

$$\frac{1}{A}\sqrt{\frac{\Sigma d}{2n}} \times 100\,\%$$

where d is the difference between the results of duplicate determinations n the number of duplicate determinations and A the mean of the B U T

Material

A total of 336 patients from an ophthalmic out patient department and an ophthalmic clinic were examined Their ages ranged from 14 to 90 years The percentage distribution was as follows stated for 10 year age groups 3 3–4 8–7 1–7 7–15 4–27 4–25 6–8 3–0 3 per cent i e the greatest number in the age groups of 60 and 70

Females predominated (63 7 per cent) They were approximately equally distributed over the different vehicle groups

The investigation comprised 646 eyes Of these 20 4 per cent had an abnormal anterior eye section (65 per cent aphakia 3.3 per cent keratitis 2.5 per cent exophthalmos 1 7 per cent iritis 1.5 per cent glaucoma subjected to operation etc) The remaining were eyes subjected to routine examinations or to examination for refraction anomalies etc

The initial B U T value was pathological (below 10 seconds) in 25 1 per cent The pathological cases were fairly equally distributed over the different vehicle groups and the B U T alterations did not differ from those of the normal material

Results

The results are seen in the tables Table I shows the vehicles prolonging the B U T i e stabilizing the precorneal film while the vehicles reducing the B U T have been set out in Table II Finally Table III comprises the vehicles with no statistically significant effect on the B U T

The coefficient of variation for the initial duplicate determination is stated within the individual groups It was 30 7 per cent for the total material

Table I

Vehicles increasing the stability of the precorneal film

Vehicle	B.U.T. factor increase ± SEM	Initial B.U.T. (seconds)	Coefficient of variation (per cent)	Number of eyes
Methyl cellulose 0.5 %[1]	1.36 ± 0.14	[illegible]	2.8	14
Methyl cellulose 1.5 %[0]	4.36 ± 0.72	23.6	41.4	14
Methyl cellulose 2.0 %[0]	2.43 ± 0.45	21.3	23.4	12
Polyvinyl alcohol 1.4 %[illegible]	1.89 ± 0.26	[illegible]	27.8	16
Polyvinyl alcohol 3 %[0]	2.96 ± 0.51	17.4	33.0	11
Polyvinyl alcohol 10 %[0]	7.16 ± 2.48	21.8	15.3	12
Polyvinyl alcohol 20 %[0]	2.82 ± 0.57	24.4	50.9	10
Polyvinyl alcohol 40 %[0]	2.30 ± 0.81	35.1	21.3	11
Adapt[3]	5.13 ± 1.34	17.5	33.[illegible]	30
Adapettes[4]	3.01 ± 0.81	11.[illegible]	36.1	20
Adsorbotear[5]	2.4[illegible] ± 0.32	17.0	42.6	25
AdsorboNaCl 5 %	2.55 ± 0.66	21.7	50.8	15
Carbowax No. 1500	2.12 ± 0.21	16.3	[illegible]	21
Dextran 10 %	4.06 ± 0.59	20.[illegible]	20.8	11
Acetyl cysteine 20 %	1.93 ± 0.37	19.6	12.4	14

[0] no preservative nor other substance added

[1] sodium chloride and phenylmercuric nitrate 0.001 % added (oculoguttae viscosae)

[2] sodium chloride and chlorbutol ½ % added (liquifilm tears)

[3] hydroxyethyl cellulose 0.44 %, B.P. adsorbobase, thiomerosal 0.002 %, EDTA 0.05 %

[4] B.P. adsorbobase, thiomerosal 0.001 %

[5] polyvinyl pyrrolidine 1.67 %, B.P. adsorbobase, hydroxyethyl cellulose 0.44 %, thiomerosal 0.002 %, EDTA 0.05 %

Mucomimetics

Methyl cellulose (MC) is usually employed in a 0.5 % concentration in the treatment of keratoconjunctivitis sicca. At this concentration the B.U.T. value was raised significantly by the factor 1.36.

Higher concentrations prolonged the B.U.T., which became four times longer at a concentration of 1.5 %. The difference is significant ($P < 0.001$).

Table II
Vehicles reducing the stability of the precorneal film

Vehicle	B U T factor reduct ± SEM	Initial B U T (seconds)	Coefficient of variation (per cent)	Number of eyes
Petroleum jelly	3 81 ± 0 81	25 0	16 3	12
Stearin	2 1, ± 0 33	11 6	38 0	10
Petrol jelly and liquid paraffin[1]	5 44 ± 0 78	24 2	24 5	20
Petrol jelly liquid paraffin and emulgator)	1 ,9 ± 0 21	20 0	33 3	12
Cetacean ointment[3]	3 09 ± 1 04	18 9	14 0	12
Cosmea moisture cream[4]	5 32 ± 1 32	18 1	54 0	15
Wool fat w water[9]	4 19 ± 1 07	22 8	16 0	10
Glycerol ointment[5]	1 83 ± 0 17	15.5	33 6	26
Arachis oil	1 50 ± 0 18	13 7	49 0	10
Olive oil	2 86 ± 0.59	20 6	26 2	10
Liquid paraffin	3 33 ± 0 53	24 7	43 8	10
Ophthasiloxan[6]	2 33 ± 0 30	19 2	21 2	10
Silicone oil 20 %[7]	3 72 ± 0 63	23.5	28 7	13
Silicone oil 100 %	4 6, ± 0 69	2 0	11.5	10
Antifoam A	7 23 ± 1 26	27 9	28.3	12
Benzalkonium chloride 0 01 %[8]	1 90 ± 0 26	29 4	35 0	2,
Cocaine 2 %	1 47 ± 0 10	15 9	28 8	18
Cocaine 4 %	1 ,2 ± 0 15	11 0	26 7	11
Albumen film on cornea	2 19 ± 0 27	23 6	48 0	14

[1] 80 % petroleum jelly and 20 % liquid paraffin (simple eye ointment Ph Nord 63)
[2] 80 % petroleum jelly 20 % liquid paraffin *with* emulgator (simple eye ointment Ph D 48)
[3] white wax spermacet arachis oil and water (cold cream)
[4] wool fat emulgator monostearin propylene glycol water preservatives
[5] glycine and wheat starch
[6] octylphenol polyoxyethylene 0 025 g distearate of polyethylene glycol 0 05 g di methyl polysiloxan q s ml 10
[7] in simple eye ointment
[8] with 0 9 % sodium chloride added
[9] 25 % water content

Table III

Vehicles with no significant effect on the stability of the precorneal film

Vehicle	Tendency	B.U.T. factor ± SEM	Initial B.U.T. (seconds)	Coeff. of variation	Number of eyes
Sodium chloride 0.9 %	fall	1.39 ± 0.20	17.0	14.6	14
Sodium chloride 5 %	rise	1.36 ± 0.17	20.1	9.0	13
Ultracortenol susp.1)	rise	1.07 ± 0.11	10.4	29.4	10
Gelatin powder 2)	fall	1.34 ± 0.20	19.4	15.0	10
Glycerine 100 %	fall	1.14 ± 0.13	22.0	30.0	14
Glucose 50 %	fall	1.74 ± 0.50	28.4	37.6	10
Cotton plug in inf. fornix	fall	1.72 ± 0.29	20.8	30.9	14
pH buffer 9.2 4)	fall	1.78 ± 0.46	18.4	61.3	12
pH buffer 10.0 5)	fall	1.83 ± 0.49	24.0	57.0	16
Exploration cream 3)	fall	4.14 ± 1.95	22.7	44.0	21

1) microcrystalline suspension of prednisolone acetate 0.5 % with sodium chloride, sodium phosphate and benzalkonium chloride added
2) sieve 0.7 mm
3) glycerol 16.5 % boric acid tragacanth mucus
4) sodium borate buffer with phenetanol 0.5 % added isotonic
5) sodium borate buffer adjusted with NaOH slightly hypertonic

At still higher concentrations (3 %, 4 %, 5 % and 10 %) the MC was so thick that it could not pass through a pipette but had to be applied with a glass rod. It mixed poorly with the precorneal film in which lumps and air bubbles were seen. At higher MC concentrations than 1.5 % the B.U.T. decreased with rising concentrations (the decrease between 1.5 % and 2 % was significant $P < 0.05$).

So the BUT increase is not only a function of the viscocity of the vehicle.

Polyvinyl alcohol (PVA) is generally used in a concentration of 1.4 %. This was found to prolong the B.U.T. significantly by the factor 1.89 (Table I). Rising concentrations prolonged the B.U.T. until a concentration of 10 % PVA which gave a seven times increase of the B.U.T. ($P < 0.05$).

An additional rise of the PVA concentration caused a reduction of the B.U.T. 20 % PVA easily passed through the pipette while 40 % was of an excessively viscous consistency.

Idapt Adapettes and *Adsorbotears* are artificial tears which prolonged the B U T though not more so than optimum concentrations of MC and PVA (The results of our investigations harmonize with those of Lemp et al (1975a) The latter having however been represented graphically without SEM no comparison *is permissible between the groups On the other hand the duration of* the effect has not been recorded in the present study)

Addition of 5 % sodium chloride to Adsorbotears did not seem to alter the effect of this on the B U T

Other substances prolonging the B U T

Dextran in a 10 % concentration is a hyperosmotic polysaccharide used as a plasma substitute It prolongs the B U T to the same extent as optimal concentrations of MC and PVA

Polyethylene glycol (Carbowax 1500 Macrogol) is a viscous fat free ointment which prolongs the B U T more than both MC and PVA in the current concentrations

Acetyl cysteine (Mucomyst 20 %) is a mucosolvent collagenase inhibiting compound It prolongs the B U T equally as long as both MC and PVA in the current concentrations

Ointments

Fatty ointments reduce the B U T (Table II) Holes soon occur in the precorneal film with resulting exposure and desiccation of the cornea

The most commonly used ointment in Scandinavia (simple eye ointment Ph Nord 63) is a mixture of 80 % petroleum jelly and 20 % liquid paraffin

This ointment has a significant greater effect than the corresponding emulsion (simple eye ointment with emulgator Ph D 48 $P < 0.001$)

On the other hand no significant difference was seen for water in oil *versus* oil in water emulsion

Stearin did not melt at the corneal temperature but remained in the form of flakes in the precorneal film Holes soon occurred sometimes close to a stearin flake and sometimes distant from this The B U T was reduced in the same manner and to the same extent as by an indifferent albumen film (piece of egg albumen membrane) placed in the precorneal film

Petroleum jelly melted and spread as drops across the precorneal film It has a greater tendency to reduce the B U T than stearin The softer simple ointment without emulsifier reduced the B U T as much as petroleum jelly

The *fat free* ointment unguentum glyceroli reduced the B U T twice only

Oils

Oil liquefies at room temperature Instilled oil was seen to spread at a faster rate over conjunctiva and cornea than ointment Oil had a significantly reducing effect on the B U T (two or three times)

Arachis oil caused less damage than olive oil and liquid paraffin ($P < 0\,01$ and $P < 0\,05$ respectively) Arachis oil had the same effect as the mild simple ointment emulsion (petroleum jelly liquid paraf with emulgator Ph D 48)

So the reduction of BUT is not only a question of the melting point

Silicone

Antifoam A is a silicone containing ointment which reduces the surface activity (raises the surface tension) The B U T was found to be reduced very considerably more than with 20 % and 100 % silicone oil and to the same extent as with non emulsified simple ointment

Ophthasiloxan has been specially prepared for the purpose of increasing the evaporation from an intact cornea The B U T was however reduced less by this compound than by Antifoam A

Other substances reducing the B U T

Cocaine surface anaesthesia reduced the B U T, though no more than the simple ointment emulsion

Benzalkonium chloride in the usually employed concentration as a preservative reduced the B U T (Table II) This bore out Wilson s result

Benzalkonium chloride in a high – toxic – concentration (0 5 %) effected pronounced micropunctate fluorescein staining This phenomenon rendered B U T reading difficult and may perhaps explain why we found a prolonged B U T (2 09 ± 0 40 11 eyes)

Drugs having no influence on the B U T

The vehicles found to be without any significant influence on the B U T have been set out in Table III

As might be expected the B U T was unaffected by physiological saline

Various hyperosmotic vehicles did not alter the B U T (5 % sodium chloride 100 % glycerin 50 % glucose)

Evidently a cotton plug placed in the inferior fornix did not absorb enough to alter the B U T

A microcrystalline suspension and a gelatin powder floating in the precorneal film did not alter the B U T

An alkaline buffer (pH 10) is a mucosolvent though not sufficiently so to alter the B U T

Vital staining

After introduction of a vehicle and subsequent B U T reading vital staining was performed with a mixture of 1 % fluorescein and 1 % rose bengal (Norn 1974)

As stated above a high benzalkonium chloride concentration (0 5 %) gave a pronounced widespread micropunctate fluorescein staining indicating damage and breach of continuity of the epithelium (cf Tønjum 1975) No rose bengal staining was seen

Fatty ointments oils and silicone gave punctate irregularly grouped often lacuna like rose bengal staining of the cornea and the adjacent exposed part of the bulbar conjunctiva Only slight fluorescein staining was seen The vital staining was in some instances so pronounced as to resemble that in kerato conjunctivitis sicca

The reduced B U T caused desiccation of the exposed part of the epithelium

MC and PVA prolonged the B U T They provoked no vital stainable phenomena not even in high concentrations

Discussion

Unfortunately the above procedure (B U T) has a fairly high coefficient of variation Lemp et al (1970) on clinical examination overcame this problem by employing the average of five readings in the individual clinical case Sauter (1976) even undertook ten readings We have employed no more than two plus two (before and after application of the vehicle) to avoid tiring the patient too much

On the other hand B U T reading is the most direct and simple method of examination for the purpose of assessing the precorneal film under practical clinical conditions Many well known vehicles influence the B U T so much (about 300–400 per cent) that the changes are demonstrable even though the coefficient of variation is high (about 30 per cent)

The stability of the precorneal film is increased by MC and PVA A maximum increase is obtained by a high concentration of PVA (10 %) without the liquid becoming too viscous The increase effected by raising the MC concentration is

more limited (maximum at 1 5 %) The B U T can also be prolonged by using fat free ointment (Macrogol) or hyperosmotic polysaccharide (Dextran) and others

These factors are of importance in the treatment of pemphigoid and kerato conjunctivitis sicca in protection of the cornea and where the period of contact of drugs is concerned

It is worth noting that ordinarily employed ointments and oils reduce the stability of the precorneal film This harmful effect is demonstrable by rose bengal staining Such substances are therefore contra indicated in pemphigoid and keratoconjunctivitis sicca

Ointment is used to protect the cornea from evaporation However protection is only yielded in the cases where the patient cannot blink (facial nerve palsy during sleep and under a bandage) In all other cases blinking will provoke holes in the ointment layer covering the cornea with resulting desiccation in spots (Norn 1976)

In corneal oedema with intact epithelium the oedema can be reduced by accelerating the evaporation This can be effected by shortening the B U T e g by means of silicone containing drugs

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References

Bach F Riddel G Miller C Martin J A & Mullins J D (1970) The influence of vehicles on neomycin sulfate prevention of experimental ocular infections in rabbits *Amer J Ophthal 68* 659–669

Hardberger R Hanna C & Boyd C M (1975) Effects of drug vehicles on ocular contact time *Arch Ophthal (Chicago) 93* 42–45

Krishna N & Brow F (1964) Polyvinylalcohol as an ophthalmic vehicle *Amer J Ophthal 57* 93–106

Krishna N & Mitchell B (1965) Polyvinyl alcohol as an ophthalmic vehicle *Amer J Ophthal 59* 860–864

Lemp M A Holly F J Iwata S & Dohlman C H (1970) The precorneal tear film *Arch Ophthal (Chicago) 83* 89–94

Lemp M A & Hamill J R (1973) Factors affecting tear film break up in normal eyes *Arch Ophthal (Chicago) 89* 103–105

Lemp M A Goldberg M & Roddy M R (1975a) The effect of tear substitutes on tear film break up time *Invest Ophthal 14* 255–258

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CLUSTER HEADACHE SYNDROME AND MIGRAINE

Ophthalmological Support for a Two entity Theory

BY

I HORVEN and O SJAASTAD

Patients suffering from migraine cluster headache and atypical cluster headache including patients with chronic paroxysmal hemicrania were studied with respect to corneal temperature intraocular pressure and corneal indentation pulse amplitude changes during pain attacks Significant rises in these three parameters were demonstrated during attacks of cluster headache and atypical cluster headache indicating that intraocular vasodilatation with increased ocular blood flow occurs during attacks No definite changes were found in migraine The results strongly suggest that significant pathophysiological differences exist between migraine and cluster headache The point is stressed that these disorders probably represent separate pathogenetic entities and should be classified as such and not be grouped together within an ill defined group of vascular headache

Key words cluster headache – corneal indentation pulse – corneal temperature – dynamic tonometry – headache – histaminic cephalgia – Horton s headache – intraocular pressure – migraine – ocular tension – pain – temperature

Although ocular symptoms are prominent during attacks of cluster headache (Horton s headache Horton et al 1939) this headache has attracted surprisingly little attention in ophthalmological circles Previously the term histaminic

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cephalgia" was used as suggested by Horton since histamine injections were believed to terminate the pain attacks in a given bout However the effect of histamine treatment has not been reproducible in the hands of other investigators and the term "histaminic cephalgia" is therefore no longer in general use In comparison with migraine cluster headache is relatively rare The mean age of onset of symptoms is around 25 years About 85–90 % of the patients are males Characteristically the pain attacks occur in clusters i e after a period of months or years without symptoms a period (or bout) with symptoms sets in usually lasting from a few weeks to several months During a bout pain attacks occur 1–4 times daily with pain free intervals between attacks (paroxysms) Occasionally pain free days even occur during a bout The pain is always unilateral and is located around or behind the eye The pain is almost invariably located on the same side Occasionally in subsequent bouts the pain may shift to the other side The pain onset is rather abrupt the pain at its maximum being extremely severe It usually lasts from 10–15 min to a couple of hours Typically a nocturnal predominance of attacks exists and the patient is awakened from his sleep by the pain During attacks slight bradycardia may occur Nasal stenosis conjunctival hyperaemia chemosis and lacrimation may be present on the symptomatic side Occasionally miosis and slight ptosis occur as in Horner s syndrome However contrary to what is found in Horner s syndrome a slight protrusion of the bulb may be seen which could hypothetically be caused by orbital hyperaemia The visual acuity is usually intact during attacks although a transient slight decrease has been observed in some patients (Sutherland & Eadie 1972) Scintillations do not occur nausea and vomiting are rarely present A normal EEG is usually found both during and between attacks (Hazan et al 1976) The mentioned ocular signs are useful in distinguishing this disorder from trigeminal pain

The question as to whether cluster headache is a separate clinical entity or a migraine variant has given rise to much controversy Arguments supporting both views still flourish The topic has been delt with in several recent communications (Bickerstaff 1968 Ekbom 1970 1974 Graham 1972 Hørven et al 1971 1972 Lance & Anthony 1971a Sutherland & Eadie 1972 Wolff 1972) Although definite evidence in favour of the two entity theory is at present lacking there is ample evidence that there is a different localization of the pathological process in the two clinical conditions (Broch et al 1970 Ekbom & Greitz 1970 Hørven et al 1972 Skinhøj 1973 Sjaastad 1975) The blood circulation of the eye seems to be affected in cluster headache (Hørven et al 1972) whereas in migraine the intracerebral blood circulation seems to be more conspicuously affected than that of the eye Information as to the nature of the primary pathological process in migraine and cluster headache is scanty

Nevertheless there are indications that the primary pathological process in the two clinical pictures may also differ the pathological process in migraine not necessarily being *primarily* vascular in nature (for details see Sjaastad 1975) The present authors feel that the balance of evidence favours the concept that migraine and cluster headache are different disorders In the present study further ophthalmological evidence for differentiation between migraine and cluster headache will be presented In previous studies (Broch et al 1970 Hørven et al 1972) some patients were included which subsequent studies (Sjaastad & Dale 1974 Sjaastad et al 1976a) have shown to be cases of atypical cluster headache In the present study such atypical cases will be treated separately

Material

Cluster headache Eighteen patients (Cases 1–18) with typical cluster headache were examined There were 3 women and 15 men with an average age of 53 5 (26–77) years Twelve had right sided and six left sided pain attacks

Atypical cluster headache Six patients (Cases 19–24) were included Cases 19–21 suffered from the recently described disorder Chronic paroxysmal hemicrania (CPH) (Sjaastad & Dale 1974) They were all females their ages ranging from 28–60 years Case 22 a female aged 39 suffered from cluster headache with recurring bouts of homolateral retrobulbar neuritis (Sjaastad et al 1976a) Cases 23 and 24 (men aged 44 and 64) are also listed as atypical cluster headache patients They demonstrated marked interparoxysmal EEG changes during bouts and had less clear cut attacks than is usually seen

In order to facilitate the presentation these patients are presented as one group This was permissible since data obtained in these patients were fairly similar It should be remembered however that this group of atypical cases may consist of at least three different disorders The statistical evaluation should be interpreted accordingly

Migraine Twenty two patients (Cases 25–46) with an average age of 36 6 (12–58) years were examined between and during pain attacks There were 13 women and 9 men 13 suffered from classical migraine and 9 from common migraine Five of the patients with classical migraine were also examined both during the scintillation period and during the subsequent pain attack

Four of the patients had bilateral headache In these patients the right eye figures are listed as symptomatic side figures in the tables This was permissible as no side difference existed between the two eyes of these patients neither between nor during pain attacks

Methods

Dynamic tonometry Dynamic tonometry was carried out in all patients during and between attacks The dynamic tonometer (Hørven 1968) is an improved standardized electronic Schiøtz tonometer that records eye tension and corneal indentation pulse (CIP) amplitudes at all tension levels The output is 1 mV (± 1 %) per micron of tonometer plunger movement (Hørven & Gjønnæss 1972) The output is linear An output of 50 mV therefore corresponds to 50 μ of plunger deflection i e one scale reading Schiøtz

The CIP amplitudes recorded by dynamic tonometry reflect the pulse synchronous alterations in intraocular pressure (IOP) This is again dependent on the pulse synchronous change in intraocular volume (ΔV) caused by the extra amount of blood which enters the eye during systole An increased pulse rate usually *creates a decrease in CIP amplitudes (Hørven & Gjønnæss 1974)* The pulse synchronous change in intraocular volume (ΔV) may be calculated in mm³ from the CIP amplitudes by the use of converting tables based on Langham s and Heland Eriksen s data (Hørven 1970a) Multiplication with the exact pulse rate gives the ΔV per min The IOP in mmHg was calculated from the *tonometer readings (5 5 gm plunger weights) by use of Friedenwald s 1955* converting tables (Friedenwald 1957)

Table I
Dynamic tonometry Reproducibility of the method

Case	CIP amplitude in μ			Pulse rate			ΔV per min		
	Average of three recordings	Range in per cent minus	plus	Average of three recordings	Range in per cent minus	plus	Average of three recordings	Range in per cent minus	plus
A	22 9	0 4	0 4	48 2	0 2	0 4	110 2	0 5	0 4
B	39 0	1 8	1 8	98 3	0 1	0 1	497 7	1 7	1 7
C	17 0	4 1	2 4	65 7	0 8	1 5	106 8	4 8	2 9
D	28 4	5 6	9 2	52 5	2 1	1 5	145 0	5 4	9 8
E	19 8	4 0	6 1	87 7	2 3	1 1	205 1	3 1	3 6
F	25 5	3 5	4 3	97 1	1 1	2 2	240 4	1 7	3 1
G	46 4	0 9	1 3	54 1	0 9	1 3	247 3	1 3	1 7
H	29 4	2 0	1 7	56 0	2 7	2 0	159 5	4 6	2 6
Average	28 6	2 8	3 4	70 0	1 3	1 3	214 0	2 9	3 2

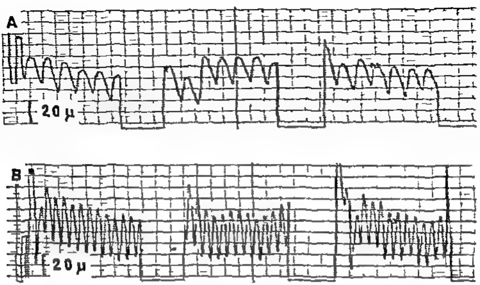

Fig. 1

Dynamic tonometry. Reproducibility of the method. Repeated examinations of Case A and Case B (Table I). Paper speed 5 mm per second.

The reproducibility of the method was tested in 8 subjects by calculating the ± range in per cent from the average value of three subsequent recordings (Table I, Fig. 1). With few exceptions, the reproducibility was better than ± 5%. The coefficient of variation (r_{v}) was calculated from the first and second sequence of these recordings by use of the formula $SD = \sqrt{\frac{\Sigma d}{2(n-1)}}$ and $r_{v} = \frac{SD \cdot 100}{\bar{x}}$ where d is the difference between the two recordings and $\bar{x}$ the mean of the observed range. The values of r_{var} were 3.2 and 2.6 respectively for the CIP amplitude and [illegible] per min results which demonstrates that the reproducibility of the method is excellent. Another way to test the reproducibility is to compare the results from the right and left eyes of normal subjects. This has been done previously and an excellent correlation was found (r = 0.997) (Hørven 1970b).

Corneal temperature registration. The corneal temperature was recorded by a specially constructed thermometer probe (Hørven & Larsen 1975) and a Brush Mark 220 recorder. The equipment yields an output of 13.6 mV per °C. With a recorder sensitivity setting of either 5 or [illegible] mV per paper division, the tem

perature tracings can be read with an accuracy of 0 2°C or less than 0 1°C respectively (Horven & Larsen 1975)

Statistical evaluation The statistical method of paired comparison and the Wilcoxon White two sample ranks test were employed

Results and Comments

Intraocular pressure (IOP) (Table II) During pain attacks a statistically significant increase in IOP took place on the symptomatic side in patients with cluster headache ($P < 0\ 005$) A similar trend was also noted in the atypical cluster headache group (Table II) whereas no change in IOP occurred in the migraine groups

In two of our patients with CPH (Cases 19 and 21) the time between normal state and peak pain was less than 1 min Case 19 had very frequent attacks and Case 21 could precipitate attacks by turning her head This gave the opportunity of recording the eye tension before and just after onset of pain (Broch et al

Table II
Intraocular pressure (mmHg)

	Between pain attacks			During pain attacks			
	Symptomatic side	Other side	*t* value*	Symptomatic side	Other side	*t* value*	
Cluster headache (N = 18)	1[illegible] 3	12 1	0 ,56 –	13 7	11 9	3 411	$P < 0\ 005$
Atypical cluster headache (N = 6)	*12 8*	*12 8*	*0* –	*15 5*	*14 1*	*1 998*	–
Migraine (N = 22)	14 5	14 5	0 208 –	14 9	14 6	1 128	–
	During scintillation						
Classic migraine (N = 5)	15 0	15 1	0 147 –	14 5	14 9	0 370	–

* Statistical method of paired comparison

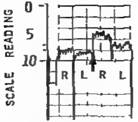

Fig 2

Eye tension recorded before and 15 seconds after onset of pain (arrow) in Case 21 atypical cluster headache right side R = right eye L = left eye A right sided eye tension increase from scale reading 8 to 5 5 is observed (5 5 gm plunger load) which corresponds to an increase in intraocular pressure from 10 2 to 15 9 mmHg

1970 Sjaastad et al 1976b) The result from Case 21 is shown in Fig 2 A marked rise in IOP was noted less than 60 seconds after pain onset in both patients averaging about 5–6 mmHg on the symptomatic side and 2 5–3 mmHg on the other side

In CPH patients the IOP slowly decreases with time during an attack until equilibrium between the two sides is obtained after 15–20 min Sometimes just after an attack the IOP on the symptomatic side might even be lower than on the other side Thus an effect similar to that seen during tonography occurs although the initial intraocular pressure rise is not induced by an external force such as the tonometer weight but by a factor inside the eye

In order to initiate a rise in IOP of 5–6 mmHg an increase of about 12 mm^3 in intraocular volume is necessary (Hørven 1970a) Changes in aqueous humour formation or drainage can not be held responsible for the observed rise in IOP since it develops too rapidly simultaneous with the onset of pain Measurable changes in ocular rigidity did not occur Accordingly the most likely explanation for this sudden increment in IOP is an acute vasodilatation with a corresponding increased volume of the intraocular vascular bed

CIP amplitudes (Table III) No change in CIP amplitudes was found during migraine attacks The CIP amplitudes were of equal size in the two eyes and averaged about 25 μ ($\pm$ 7 5 = 1 SD) (range 9–42) which is slightly less than the normal average of 30 μ ($\pm$ 10 0 = 1 SD) (range 13–56) (Hørven 1970b)

Amplitudes of similar size to those observed in migraine were found in the inter paroxysmal period in patients with ordinary cluster headache This is a new observation (In previous studies (Hørven et al 1972) larger values were listed as our cluster headache group also included some atypical cluster headache

Table III
Corneal indentation pulse amplitudes (μ)

	N	Between pain attacks				During pain attacks			
		Symptomatic side	Other side	t value*		Symptomatic side	Other side	t value*	
Cluster headache	18	23 6	23 0	1 401	–	34 8	23 3	4 744	$P<0\ 001$
Atypical cluster headache	6	44 2	40 5	2 412	–	41 7	58 5	5 519	$P<0\ 001$
Migraine	22	26 0	25 5	1 308	–	25 1	24 4	1 001	–
		During scintillation							
Classic migraine	5	24 8	24 8	0	–	25 4	24 9	0 012	–

	N	Symptomatic side				Other side			
		Between pain attacks	During pain attacks	t value*		Between pain attacks	During pain attacks	t value*	
Cluster headache	18	23 6	34 8	5 267	$P<0\ 001$	23 0	25 3	3 290	$P<0\ 005$
Atypical cluster headache	6	44 2	71 7	4 292	$P<0\ 005$	40 5	58 5	3 473	$P<0\ 02$
Migraine	22	26 0	25 1	1 168	–	25 5	24 4	1 093	–
		During scintillation				During scintillation			
Classic migraine	5	24 8	25 4	0 440	–	24 8	24 8	0 094	–

* Statistical method of paired comparison

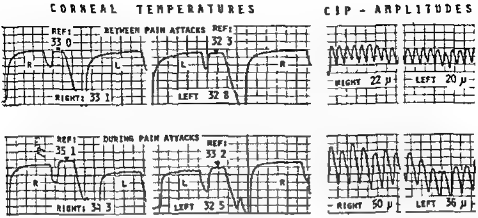

Fig 3

Increase in corneal temperature (+°C) and corneal indentation pulse (CIP) amplitudes during pain attack of Case 94 atypical cluster headache right side
REF = reference temperature

patients with larger CIP amplitudes) During pain attacks however a statistically significant increase was demonstrated most pronounced on the symptomatic side (Table III) This is in accord with previous findings (Horven et al 1972)

The co existence of attacks and increased CIP amplitudes most pronounced on the symptomatic side was also demonstrated in the atypical cluster headache group However the atypical cluster headache patients showed CIP amplitudes which were about twice as large as those observed in ordinary cluster headache patients in most cases also between attacks (Fig 3 Table III) As judged by the Wilcoxon White two sample ranks test this difference was statistically significant (Cluster headache (N = 18) versus atypical cluster headache (N = 6) Between attacks symptomatic side 184/18–116/6 $P < 0\,01$ other side 185 5/18–114 5/6 $P < 0\,01$ During attacks, symptomatic side 175.5/18–124 5/6 $P < 0\,01$ other side 174 5/18–125 5/6 $P < 0\,01$) It should be remembered however that the atypical cluster headache group is heterogenous

Thus the CIP amplitude pattern to some extent seems to distinguish atypical cluster headache patients from ordinary cluster headache patients The larger CIP amplitudes in most of the atypical cases both between and during attacks suggest either a larger intraocular vascular bed in these patients or a true difference in the pathogenesis of these disorders Accordingly such atypical cases should be classified and listed separately from ordinary cluster headache patients

Pulse rate (Table IV) In most of our cluster headache patients a slight brady cardia was demonstrated during pain attacks This is a typical finding in this disorder The same applied to atypical cluster headache patients A significant increase in pulse rate was noted during the scintillation (teichopsia) phase of classic migraine Most probably this latter observation may be explained by the fact that the patients had to hurry to get to the eye clinic for examination before the scintillation phase ended An increased pulse rate caused by physical exercise should be accompanied by an increase in cardiac stroke volume and ΔV per min (Horven & Gjonnæss 1974) If the above explanation is valid an increase in ΔV per min should be expected during the scintillation phase Such an increase was *observed* (*Table V*)

ΔV per minute (Table V) No side difference was found in migraine neither between nor during attacks There was a slight but significant increase in ΔV per min during the scintillation phase in classical migraine This increment may best be explained by the increased pulse rate as mentioned above

A statistically significant side difference was present during attacks both in cluster headache and in atypical cluster headache with larger values on the symptomatic side (Table V) When the results obtained between attacks were compared with the increased values obtained during attacks a statistically significant difference was found *most pronounced on the symptomatic side* (Table V)

If a bradycardia should occur at rest the CIP amplitudes will increase correspondingly the product CIP amplitude · Pulse rate being fairly constant

Table IV
Pulse rate

	Between pain attacks	During pain attacks	*t* value*	
Cluster headache (N = 18)	72 9	67 9	1 826	–
Atypical cluster headache (N = 6)	69 3	65 0	0 884	–
Migraine (N = 2[illegible])	71 0	76 2	1 017	–
	During scintillation			
Classic migraine (N = 5)	87 8	71 1	3 356	$P < 0\ 05$

* *Statistical method of paired comparison*

Table V
ΔV per min (mm³/min)

	N	Between pain attacks				During pain attacks			
		Symptomatic side	Other side	t value*		Symptomatic side	Other side	t value*	
Cluster headache	18	159.9	157.3	0.839	–	219.7	177.1	4.790	$P<0.001$
Atypical cluster headache	6	294.7	267.5	3.018	$P<0.05$	453.3	370.7	5.860	$P<0.001$
Migraine	22	176.1	172.5	1.505	–	180.7	176.4	1.750	–
		During scintillation							
Classic migraine	5	217.9	219.9	1.553	–	175.4	168.6	1.362	–

	N	Symptomatic side				Other side			
		Between pain attacks	During pain attacks	t value*		Between pain attacks	During pain attacks	t value*	
Cluster headache	18	159.9	219.7	5.813	$P<0.001$	157.3	177.1	3.098	$P<0.01$
Atypical cluster headache	6	294.7	453.3	4.569	$P<0.005$	267.5	370.7	3.358	$P<0.02$
Migraine	22	176.1	180.7	0.905	–	172.5	176.4	0.655	–
		During scintillation				During scintillation			
Classic migraine	5	217.2	175.4	4.618	$P<0.01$	212.2	168.6	7.710	$P<0.005$

* Statistical method of paired comparison

Table VI
Corneal temperature in +°C

Case No	Cluster headache					
	Between pain attacks			During pain attacks		
	Symptomatic side	Other side	Diff	Symptomatic side	Other side	Diff
10	33 8	33 7	0 1	34 2	33 7	0 5
11	33 2	33 1	0 1	33 4	32 5	0 9
13	32 5	32 3	0 2	34 9	33 5	1 4
14	32 4	32 6	–0 [illegible]	33 9	32 7	1 2
15	32 7	33 0	–0 3	33 6	32 8	0 8
17	34 65	34 8	–0 15	35 3	33 15	0 15
18	32 15	32 1	0 05	32 2	31 4	0 8
Average	33 06	33 09	–0 03	33 93	33 11	0 82
t value *	0 407			5 229	$P<0\ 005$	
	Atypical cluster headache					
19	34 5	33 8	0 7	35 4	33 4	2 0
21	34 75	34 0	0 75	35 0	33 9	1 1
24	33 1	32 8	0 3	34 3	32 5	1 8
Average	34 16	33 53	0 63	34 9	33 27	1 63

* Statistical method of paired comparison

(Horven & Gjønnæss 1974) Thus the increased ΔV per min during pain attacks in these groups of patients clearly demonstrates that the CIP amplitude increment by far outweighs the bradycardia effect Accordingly the increment in amplitudes can not be explained by the bradycardia alone a factor which should affect the non symptomatic side to the same degree as the symptomatic side

Corneal temperature registration (Table VI) Pilot studies of patients with common and classical migraine showed no alteration in corneal temperature during scintillation or pain attacks

In ordinary cluster headache no side difference was found in the period between pain attacks The average corneal temperature was +33 1°C which is slightly less than the control average of +33 7°C (Horven 1975) During pain attacks the corneal temperature was significantly increased on the symptomatic side (Table VI) Similar findings were observed in the atypical cluster headache patients In addition these patients also demonstrated higher corneal tempera tures on the symptomatic side between attacks The difference increased markedly during pain and averaged +1 63°C A typical recording is shown in Fig 3

Theoretically a rise in corneal temperature could be initiated by excessive tearing (Mapstone 1968) by heat conducted to the cornea from the surrounding tissue from the ciliary body or from the posterior part of the eye The warm tears could possibly affect the registration directly but this seems rather unlikely as the contact probe used for registration is specially constructed to shield it from the influence of tears The temperature sensor is located in the very centre of the 3 mm diameter probe tip (Hørven & Larsen 1975)

Alternatively warm tears could conduct heat to the corneal stroma itself in which case a rise in corneal temperature would be expected following lacrimation This possibility was tested in 8 normal subjects with the following results Average corneal temperature before lacrimation right 34 74°C left 34 61°C Following three min excessive tearing precipitated by mechanical irritation of the nasal mucosa in the right nostril right 34 78 C left 34 40 C Accordingly the effect of lacrimation seems small and could if at all probably account for only a minor part of the temperature increase demonstrated during pain attacks in our patients

Another possibility may be that heat is conducted to the cornea from the surroundings Horton et al (1939) found a +1–3°C rise in cutaneous temperature in the temporal region on the symptomatic side in cluster headache patients However Lance & Anthony (1971b) have even found cold patches around the eye on the symptomatic side during the early phase of pain attacks in some cluster headache patients a finding which does not support this hypothesis Cutaneous temperature registrations have not been performed during pain attacks in CPH patients

Therefore the most likely explanation for the observed rise in corneal temperature during pain attacks of cluster headache and atypical cluster head ache patients is that the acute intraocular vasodilatation which presumably exists as judged from the dynamic tonometry results is accompanied by an increased blood flow through the eye The arterial blood is pre heated to about +37 0°C in the thoracic cavity An increased blood flow through the eye will tend to reduce the temperature gradient between the posterior and anterior

parts of the eye Experimentally a rise in ocular temperature of +2–4°C was obtained in cats and dogs by compression of the abdominal aorta thus forcing more pre heated blood to the animals eyes (Colle et al 1931) A frequent rise in temperature as in the CPH patients with 6–18 pain attacks a day can theoretically explain the fact that the cornea is also warmer on the symptomatic side between attacks as was demonstrated (Table VI) The possibility also exists that a low grade constant increase in ocular blood flow is present on the symptomatic side between attacks in this group of patients

General Comments

The present study demonstrates major differences between the migraine and *cluster headache groups of patients In migraine the small alterations noted* during scintillation can well be explained by the fact that the patients hurried to get to the ophthalmological department for examination before the symptoms subsided

In cluster deadache the CIP amplitude and ΔV per min were somewhat smaller than normal before attacks During pain however they increased by approximately 50 % on the symptomatic side together with an increase in intra ocular pressure and corneal temperature In atypical cluster headache similar but more pronounced changes took place In most of these latter cases the CIP amplitude and ΔV per min were larger than normal also between pain attacks

Could methodological errors or the fact that the patients were examined repeatedly at different times of the day and at various intervals be held responsible for the recorded changes? This possibility can probably be rejected As mentioned the reproducibility of the method is adequate usually better than $\pm$ 5 % (Table I) Previously 33 subjects were examined twice at intervals ranging from 1 day to several months A significant correlation was obtained between the CIP amplitude results of the two examinations ($r = 0\ 801$ $P < 0\ 001$) (Hørven 1970b) When six women were examined repeatedly during one menstrual cycle the intra individual variations in ΔV per min were rather small and did not exceed $\pm$ 20 % of the average value (Hørven et al 1976) Thus the CIP amplitude and ΔV per min seem to some extent to be characteristic for the individual subject Measurable changes in ocular rigidity did not occur and the slight bradycardia which was seen during pain attacks can only explain a small fraction of the CIP amplitude increment An increase of 50 % or more as observed in cluster headache and atypical cluster headache patients during pain attacks is far beyond that which can be explained by methodological errors

or physiological variations In addition a statistically significant side difference was present during pain attacks which is never seen during physiological conditions Accordingly the changes observed in CIP amplitude and ∆V per min should be accepted as pathological characteristics of these disorders Dynamic tonometry is therefore presented as an easy and practical method which may aid in the diagnosis of patients suffering from cluster headache and atypical cluster headache

The findings may also give some clue to the pathogenesis of these disorders In the CPH patients an increase in IOP could be measured shortly after pain onset which strongly points to an intraocular vasodilatation as the mechanism behind the increased CIP amplitudes In cluster headache the IOP was significantly higher during pain attacks which makes it highly probable that a similar intraocular vasodilatation occurs also in these patients As mentioned the increase in corneal temperature could well be taken as an indication of increased ocular blood flow The mechanism behind such a dilatation of the pulsating part of the intraocular vascular bed is unknown It may well be that these changes are closely related to if not responsible for the pain itself

In migraine no signs of increased IOP were observed during the pain phase or during scintillation

The present study gives support to the concept that migraine and cluster headache are different pathological conditions In order to obtain more knowledge of these disorders and their sub groups it is important that they are listed classified and studied separately and not indiscriminately lumped together in the ill defined group of vascular headache

References

Bickerstaff E R (1968) Cluster headache In Vinken P J and Bryun G W Eds *Handbook of Clinical Neurology* North Holland Publishing Company Amsterdam *Vol 5* 111–118

Broch E Hørven I Nornes H Sjaastad O & Tønjum A. (1970) Studies on cerebral and ocular circulation in a patient with cluster headache *Headache 10* 1–8

Colle J Duke Elder P M & Duke Elder W S (1931) Studies on the intraocular pressure Part I The action of drugs on the vascular and muscular factors controlling intraocular pressure *J Physiol (Lond) 71* 1–30

Ekbom K (1970) A clinical comparison of cluster headache and migraine *Acta neurol scand 46 Suppl 41* 1–48

Ekbom K (1974) Clinical a pects of cluster headache *Headache 13* 176–180

Ekbom K & Greitz T (1970) Carotid angiography in cluster headache *Acta radiol Diagn (Stockh) 10* 177–186

Friedenwald J S (1951) Tonometer calibration An attempt to remove discrepancies found in the 1954 calibration scale for Schiøtz tonometers *Trans Amer Acad Ophthal Otolaryng 61* 108–123

Graham J R (1972) Cluster headache *Headache 11* 175–185

Hazan Z Sjaastad O & Lundervold A (1976) *An electroencephalographical investigation of patients with cluster headache Clin Electroencephal* in press

Horton B T MacLean A R & Craig W (1939) A new syndrome of vascular headache Results of treatment with histamine preliminary report *Proc Mayo Clin 14* 257–260

Horven I (1968) Dynamic tonometry I The dynamic tonometer *Acta ophthal (Kbh) 46* 1213–1221

Horven I (1970a) Dynamic tonometry II Methods of corneal indentation pulse registration *Acta ophthal (Kbh) 48* 23–38

Horven I (1970b) Dynamic tonometry III The corneal indentation pulse in normal and glaucomatous eyes *Acta ophthal (Kbh) 48* 39–58

Horven I (1975) Corneal temperature in normal subjects and arterial occlusive disease *Acta ophthal (Kbh) 53* 863–874

Horven I Nornes H & Sjaastad O (1971) Dynamic tonometry in migraine and cluster headache In *Proc Int Headache Symposium* Elsinore Denmark pp 103–110

Horven I Nornes H & Sjaastad O (1972) Different corneal indentation pulse pattern in cluster headache and migraine *Neurology (Minneap) 22* 92–98

Horven I & Gjønnæss H (1972) Corneal indentation pulse reduction in pregnancy *Acta ophthal (Kbh) 50* 375–384

Horven I & Gjønnæss H (1974) Corneal indentation pulse and intraocular pressure in pregnancy *Arch Ophthal (Chicago) 91* 92–98

Horven I & Larsen C T (1975) Contact probe for corneal temperature measurements *Acta ophthal (Kbh) 53* 856–862

Horven I Gjønnæss H & Kroese A (1976) Blood circulation changes in the eye and limbs *Acta ophthal (Kbh) 54* 203–214

Lance J W & Anthony M (1971a) Migrainous neuralgia or cluster headache *J Neurol Sci 13* 401–414

Lance J W & Anthony M (1971b) Thermographic studies in vascular headaches *Med J Austr 1* 240

Mapstone R (1968) Determinations of corneal temperature *Brit J Ophthal 52* 729–741

Simard D & Paulson O B (1973) Cerebral vasomotor paralysis during migraine attack *Arch Neurol (Chic) 29* 207–209

Sjaastad O & Dale I (1974) *Evidence for a new (?) treatable headache entity* A preliminary report *Headache 14* 105–108

Sjaastad O (1975) Vascular and biochemical findings in migraine In Saxena P R Ed *Migraine and Related Headaches* Erasmus Universiteit Rotterdam pp 55–69

Sjaastad O (1976) So called vascular headache of the migraine type One or more nosological entities? *Acta neurol scand 54* 125–139

Sjaastad O Horven I & Vennerod A M (1976a) A new headache syndrome? Headache resembling cluster headache (Horton s headache) with recurring bouts of homolateral retrobulbar neuritis partial factor XII deficiency bleeding tendency and a hetero lateral convulsive episode *Headache 16* 4–10

Sjaastad O Djupesland G Horven I Kayed K Rootwelt K Schrader H Sundby A & Veger T (1976b) *Chronic paroxysmal hemicrania a cluster headache variant 3* Some new observations In preparation

Skinhoj E (1973) Hemodynamic studies within the brain during migraine *Arch Neurol (Chic)* 29 95–98
Sutherland J M & Eadie M J (1970) Cluster headache In Friedman A P Ed *Res clin Stud Headache* 3 92–125
Wolff H G (1972) In Dalessio D Ed *Headache and other head pain* Oxford University Press New York 3rd ed

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330 TRABECULECTOMIES – A FOLLOW UP STUDY THROUGH ½–3 YEARS

BY

T JERNDAL and M LUNDSTRÖM

In 1967 a new microsurgical procedure for glaucoma known as trabeculectomy was introduced This method is reported to have few early complications and a good pressure reducing effect Our material presents the results of 330 consecutive trabeculectomies with a follow up period of ½–3 years The following items are discussed IOP visual acuity visual fields surgical complications and need of re operation and medical postoperative therapy We conclude that trabeculectomy is a safe and efficient antiglaucoma operation recommended as an attractive alternative to heavy medication

Key words glaucoma – glaucoma surgery – microsurgery – trabeculectomy – visual field defects – surgical complication

Trabeculectomy – a new surgical intervention for glaucoma was described in 1967 by Coryllos His paper was written in the Greek language and unknown to Cairns and Linner who independent of one another reported their techniques of microsurgical trabeculectomy at the 2nd International Symposium on Microsurgery of the Eye in 1968 Another early report on trabeculectomy was given by Phillips that same year

Since then trabeculectomy has proved itself to be an important advance in glaucoma treatment (Cairns 1968 Thyer & Wilson 1972 Ridgeway et al

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1972 Jerndal & Krusa 1974 Schwartz & Anderson 1974) These reports have stressed the favourable pressure reducing effect of trabeculectomy and the paucity of complications However every new antiglaucoma procedure is received with a great deal of scepticism particularly concerning the long term results Therefore we felt it motivated to present our trabeculectomy results in 330 cases after 1/2–3 years follow up Within such a lengthy period it is reasonable to assume that the early postoperative complications will be readily apparent and the long term trends e g cataract will be discernible The presentation of this material is concerned with the pressure reducing effect the complications and the postoperative changes in visual acuity and visual fields

Technique

Our surgical technique followed that described by Watson (1969) An operating microscope (Zeiss Op Mi 7) was used in all cases Peroral intake of 100–150 ml 50 per cent glycerine 30 min before surgery was used for reduction of the IOP

Conventional retrobulbar anaesthesia and akinesia was administered A large full conjunctival flap was fashioned with an incision parallel to the corneo scleral limbus At the 12 o clock position a half thickness limbus based scleral flap measuring 4 x 6 mm was prepared The lamellar dissection in the anterior direction passed the limbus and entered the corneal tissue All bleeding vessels were cauterized The incision into the anterior chamber was placed immediately in front of Schwalbe s line in clear corneal tissue As a rule the basal iris prolapsed and was perforated with release of aqueous whereafter a spontaneous reposition of the iris took place

A radial cut backwards from the right end of the corneal incision divided the trabecular band Schlemm s canal and the scleral spur The next cut was made in the sclera parallel to and just behind the scleral spur The uveal meshwork was separated from the trabecular band with open scissors and the trabeculectomy block was then released by a second radial cut at the left end of the corneal incision A broad basal iridectomy was carried out corresponding to the trabeculectomy and the scleral trapdoor was sutured with virgin silk using two stitches The conjunctiva was closed with a running 6–0 silk suture 1 per cent atropine eye drops and 1 per cent chloramphenicol ointment were instilled before padding The patient was allowed up after dressing on the first postoperative day and discharged on the sixth day

Atropine drops were continued for 5 weeks but no routine steroid therapy was given

Table I
330 trabeculectomies Sex distribution

	Males	Females	Total
Number of operated eye	146	184	330
Number of re operated eyes	12	7	

Material

Our material is composed of 330 consecutive eyes operated with trabeculectomy 146 patients are males and 184 females all caucasian (Table I)

The glaucoma diagnoses in the material are specified in Table II An explanation for the large number of late congenital glaucoma is given by the fact that we have closely followed the classification criteria given by the International Glaucoma Symposium in 1954 and referred by Duke Elder (1969) The classification of simple glaucoma is permitted only when the irido corneal angles are open and free from a) maldevelopmental signs at the angle and b) secondary changes such as exfoliation phenomenon excessive pigmentation and postuveitic synechiae According to the criteria described by Jerndal (1970) by using a meticulous gonioscopy with high magnification and narrow slit angle maldevelopment (goniodysgenesis) was found in 185 eyes and these eyes were therefore classified as late congenital glaucoma With a less accurate gonioscopic technique these cases would probably have been classified as simple glaucoma

Table II
330 trabeculectomies Distribution of specified glaucoma diagnoses

Late congenital glaucoma	185
Exfoliation glaucoma	118
Simple glaucoma	17
Pigmentary glaucoma	4
Closed angle glaucoma	5
Secondary glaucoma (uveitic)	1
	330

Our criteria for the surgical intervention

1 Glaucoma with verified visual field defects which progressed during maximal tolerable medical treatment irrespective of the IOP

2 Glaucoma with verified field defects and an IOP surpassing 25 mmHg by applanation in spite of maximal tolerable medication

Results

The following postoperative parameters are presented the reduction of IOP the visual acuity the visual fields the complications of the surgical interventions and the frequency of additional postoperative treatment (re operation or medical therapy) (Tables III–VIII)

The mean postoperative reduction of IOP was 14 4 mm by applanation (from 31 5 to 17 1 mmHg) The distribution of the reduction in different control groups is given in Table III The early tensional drop was marked the IOP 21 days after the intervention was reduced to less than 20 mmHg in almost 97 per cent

Table IV displays the tensional results of 165 eyes followed for 1½–3 years

The number of eyes that required postoperative medical treatment is indicated in Table V

The rate of re operations is indicated in Table I Re operation with a new trabeculectomy *did not infer a greater risk* for complications than did the first intervention

A detailed list of the postoperative visual results is given Table VI

Table III

330 trabeculectomies Mean postoperative reduction of IOP after trabeculectomy (330 eyes) The postoperative IOP was taken as the mean of the two latest values at ambulatory controls

Mean IOP by applanation	Period of observation (years)					
	½	1	1½	2	2½	3
Preoperative IOP	31	29	31	31	33	34
Postoperative IOP	15	15	1[illegible]	[illegible]	19	18
Number of eyes	9	86	8[illegible]	46	26	11

Table II

330 trabeculectomies Number of eyes with postoperative IOP ≤ 21 mmHg and a follow up period $\geq 1^1/_2$ years (n = 165)

Number of eyes with IOP ≤ 21 mmHg after the therapy indicated	Therapy	Period of observation (years)			
		$1^1/_2$ (82 eyes)	2 (46 eyes)	$2^1/_2$ (26 eyes)	3 (11 eyes)
	Single trabeculectomy	57	21	12	5
	Trabeculectomy combined with postop medical treatment	12	[illegible]	[illegible]	2
	Re operation (trabeculectomy)	0	3	1	2
	Re operation combined with medical treatment	0	1	0	0
	Total number of eyes with IOP ≤ 21 mmHg	69	33	19	9

Table I

330 trabeculectomies Number of eyes given postoperative medical treatment Note that after $1^1/_2$ years of follow up there is no real increase in cases requiring postoperative medical treatment

	Period of observation (years)					
	$^1/_2$	1	$1^1/_2$	2	$2^1/_2$	3
Number of eyes with postoperative medical treatment	7 (9 %)	15 (17 %)	24 (30 %)	14 (29 %)	[illegible] (33 %)	3 (2[illegible] %)
Number of eyes in each group	79	86	82	46	[illegible]6	11

Table VI

330 trabeculectomies Postoperative change of visual acuity

Period of observation (years)	1/2	1	1 1/2	2	2 1/2	3
Change of visual acuity						
> +0 4	–	3	2	–	–	–
+0 3 – +0 4	2	–	1	–	–	–
+0 1 – +0 2	10	6	5	3	–	–
± 0	46	37	35	25	13	6
–0 1 – –0 2	16	28	20	10	5	4
–0 3 – –0 4	3	7	13	2	4	1
–0 5 – –0 6	1	3	5	3	3	–
–0 7 – –0 8	–	–	–	1	1	–
> –0 8	1	2	1	2	–	–

Table VII

330 trabeculectomies Number of eyes showing postoperative progressive field loss due to glaucoma

	Period of observation (years)					
	1/2	1	1 1/2	2	2 1/2	3
Postoperative loss of field due to glaucoma	0	5	7	[illegible]	3	2
Number of eyes in each group	79	86	82	46	96	11

Table VIII
330 trabeculectomies Postoperative complications

Complications	Number	Time of occurrence
Cataract early	2	< ½ year
late	11	> ½ year
Retinal detachment	2	1 – 1½ year
Optic vasculitis	1	3 days
Endophthalmitis (cured by antibiotics)	1	1 year
Flat chamber (lasting)	2	
Malignant glaucoma	1	1 day
Asteroid degeneration of the vitreous	1	1 year
Conjunctival oedema (wound dehiscence)	1	2 days
Postop uveitis (severe)	1	10 days

As for perimetric results 20 eyes demonstrated a progressive glaucomatous loss of visual field after trabeculectomy according to Table VII Ten of these eyes had postoperative IOP s below or equal to 20 mmHg by applanation Thus there was no definite relation to high postoperative pressures but probably to a poor local or general blood circulation

A meticulous list of postoperative complications is given in Table VIII Slight hyphaemas present for a couple of days after operation were not regarded as complications

Discussion

The aim of all therapeutic efforts for chronic open angle glaucoma is to arrest the gradual process of degeneration of the optic nerve fibres If this aim is attained there will be no further development of the visual field defect and the disease can be regarded as arrested with a permanent field defect It is in accordance with every day experience that many cases of

glaucoma cannot be checked by medical treatment in the long run This was also found by Smith (1972) in a prospective study of surgical vs medical glaucoma treatment

It is also well known that successful filtering procedures have accomplished a definite arrest of the glaucomatous process by an efficient and lasting reduction of the IOP It is most important to stress the fact which is however seldom outspoken that glaucoma can be brought to a standstill by surgical treatment The current problem is to find a surgical technique for adult glaucoma that is safe and reliable enough to be recommended for a wide use in analogy with goniotomy for infantile glaucoma The experience gained from trephinations iridencleises cyclodialyses and thermal sclerotomies are varying indeed and these interventions are accompanied by several complications of which flat chamber and cataract are the most frequent

As far as postoperative cataract is concerned the factors considered to predispose to cataract are old age pre existing lens opacities and preoperative treatment with cholinesterase inhibitors (Axelsson 1966 Shaffer & Rosenthal 1970) Additional postoperative factors are often listed postoperative hypotony choroidal detachment direct surgical trauma to the lens and sudden decompression during operation

After iridencleisis Leydhecker (1972) has reported that lens opacities developed or increased in 46 % of 186 eyes 56 eyes (30 %) developed cataract within three years after the operation 17 % of the 186 eyes ended up with a visual acuity less than 0 1 due to cataract within a follow up period ranging between 1 and 10 years

After peripheral iridectomy with thermal cauterization of the sclerostomy a varying incidence of cataract is reported In a material of nearly 500 eyes Polychronakos & Chryssafis (1970) concluded that only 6 6 % developed cataract as a consequence of the surgical intervention in a control period of 20 months The overall incidence of cataract in their material however was 10 % in a period between 2 and 5 years Using a similar operation technique (Scheie s operation) Hilsdorf (1966) found postoperative cataract in 23 7 % of 112 eyes followed through 1–6 years

The new microsurgical technique of trabeculectomy has been reported to imply less frequent side effects Particularly the postoperative flat chamber with a rapid development of cataract is rare a finding corroborated in our study (Table VIII)

It is important to point out our observation that in cases requiring postoperative miotics a better reduction of IOP was obtained than preoperatively with the same topical drug A possible explanation for this finding is an improved penetration of the drug to the internal eye So postoperative topical

medical treatment is indicated and valuable for those cases in whom the trabeculectomy alone proves insufficient and a re operation is not desirable

The aim of the therapy vi the arrest of the advancing defects of the visual fields was achieved in 91 5 per cent of the material observed for more than 1½ years This figure should be evaluated in view of the mean preoperative IOP of 31 5 mmHg There was no clear trend for the field defects to progress in the later period of observation

The change of the postoperative visual acuity was positive in 32 eyes none in 162 and negative in 136 eyes as demonstrated by Table VI Loss of more *than five lines on the ten lined visual acuity chart was noted in 28 cases* 13 of which were considered to be caused directly or indirectly by the surgical intervention Only two of these cases developed lens opacities with ½ year after the operation the others showed a slow progress There was no certain relation to postoperative hypotony in the cases with slow progress At the time being 7 of the eyes with postsurgical cataract have been operated with extraction of the cataract which in every case was uneventful and resulted in an improvement of the visual acuity Especially interesting was one case of simple glaucoma in the last eye where a visual field restricted to approximately 20 x 15° was maintained after the cataract extraction resulting in a 5/10 visual acuity and a restored reading ability

A complete list of the postoperative complications is found in Table VIII There were two dreaded complications malignant glaucoma and late endophthalmitis one case of each which were fortunately relieved by prompt and adequate therapy The malignant glaucoma was treated by an acute cataract extraction and the endophthalmitis by intravenous and local antibiotics with useful vision saved in both eyes 0 8 and 0 4 respectively

Less encouraging on the other hand were two cases of persisting flat chamber the former classic complication of a filtering procedure These two cases developed cataract and posterior synechiae on the basis of a choroidal detachment and ended up with very poor vision It should be added that *no plomb application was tried at the trabeculectomy site which might have* improved the condition

Conclusion

During a follow up period of 1½-3 years the present trabeculectomy material demonstrates that a single intervention resulted in a postoperative IOP less than 21 mmHg in approximately 58 per cent (95 cases of 165) With a re operation (new trabeculectomy) or an addition of postoperative medical treat

ment the IOP was controlled (less than 21 mmHg) in another 21 per cent For the same group of cases (1½–3 years) it has also been shown that an arrest of the glaucomatous process judged by Goldmann perimetry was achieved in 91 5 per cent

These figures are regarded as encouraging in view of the fact that severely glaucomatous eyes with advanced field defects were in majority Not all of these successfully treated eyes could maintain their preoperative visual acuity mainly because of a slowly advancing cataract but it must be re membered that the mean age of the patients in the material was 66 years In 7 eyes with cataract an extraction after a limbal knife incision improved the vision in every case and offered no special technical difficulties compared to a standard extraction

The immediate true postoperative complications were very few and in fact confined to only 4 eyes No eye in the whole material was lost in the sense that enucleation was necessary

Thus it does not seem unfair to conclude in accordance with Stallard (1973) that for early glaucomatous cases trabeculectomy with a basal iridectomy is an advantageous method compared with the previous filtering operations More explicitly trabeculectomy is an attractive and efficient therapeutic alternative to heavy medication in open angle glaucoma of all classes

References

Axelsson U (1966) Glaucoma miotic therapy and cataract *Acta ophthal (Kbh) 47* 55

Cairns J E (1968) Trabeculectomy *Trans ophthal Soc U K 88* 21

Cairns J E (1970) Trabeculectomy 2nd Int Symp Ophthal Microsurg Study Group Burgenstock 1968 *Adv Ophthal 22* 143

Coryllos C (1967) Trabeculectomy A new Glaucoma Operation *Bull of the Hellen Ophthal 35* 147

Duke Elder S (1969) *System of Ophthal* Vol IX p 389 Kimpton London

Hilsdorf C (1966) Die Ergebnisse einer einfachen filtrierenden Glaukomoperation Basis excision mit Kauterization *Klin Mbl Augenheilk 148* 375

Jerndal T & Krusa V (1974) Results of trabeculectomy for pseudo exfoliative glaucoma – a study of 52 cases *Brit J Ophthal 58* 974

Jerndal T (1970) Goniodysgenesis and hereditary juvenile glaucoma *Acta ophthal (Kbh) Suppl 107*

Leydhecker W (1966) Spatergebnisse nach Iridencleisis *Klin Mbl Augenheilk 148* 818

Linner E (1970) Some experiences of microsurgical trabeculectomy and trabeculectomy ab externo in chronic simple glaucoma 2nd Int Symp Ophthal Microsurg Study Group Burgenstock 1968 *Adv Ophthal 22* 132

Phillips C I (1968) Trabeculectomy *ab externo Trans ophthal Soc U K 88* 681

Polychronakos D J & Chryssafis B (1970) Die periphere Iridektomie mit skleraler Kauterisation (Scheie che Operation) *Klin Mbl Augenheilk 157* 463
Ridgeway A E A Rubinstein K & Smith V H (1972) Trabeculectomy – a study of [illegible] cases *Brit J Ophthal 56* 511
Schwartz A L & Anderson D R (1974) Trabecular surgery *Arch Ophthal (Chicago) 92* 134
Shaffer R N & Rosenthal G (1970) Comparison of cataract incidence in normal and glaucomatous populations *Amer J Ophthal 69* 368
Smith R J H (1972) Medical versus surgical therapy in glaucoma simplex *Brit J Ophthal 56* 277
Stallard M H (1973) *Eye Surgery* 5th Ed p 619 Wright & Sons Bristol
Thyer H W & Wilson P (1972) Trabeculectomy *Brit J Ophthal 56* 37
Watson P G (1972) Surgery of the glaucoma *Brit J Ophthal 56* 299

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RELATIONSHIP BETWEEN PERIMETRIC ECCENTRICITY AND RETINAL LOCUS IN A HUMAN EYE

Comparison with Theoretical Calculations

BY

L. FRISÉN and G SCHÖLDSTRÖM

A blind but grossly normal eye was removed because of severe pain With the patient s consent photo coagulation markers were placed along the horizontal meridian of the retina prior to surgery The angular coordinates in visual space of the markers were determined by an ophthalmoscopic procedure The loci of the markers were also determined in a flat preparation following enucleation The relationship between retinal arc and perimetric eccentricity was found to be approximately linear up to at least 50 degrees Our findings validate earlier theoretical calculations within this range

Key words anatomy of the eye – optics of the eye – perimetry

The relationship between perimetric eccentricity and position on the retina is of interest in both basic research and clinical work It has been the subject of several theoretical studies employing model eyes (e g Stine 1934 Lotmar 1971 Drasdo & Fowler 1974 Frisen & Frisen 1976) For obvious reasons possibilities to verify such calculations are rare We have had the opportunity to study this relationship in an eye blind from spheno orbital meningioma

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where the patient demanded enucleation because of intolerable pain and lacrimation Except for complete optic atrophy the eye appeared normal With the patient s consent photo coagulation markers were produced along the horizontal meridian of the retina prior to surgery The perimetric eccentricities of these markers were then determined using an ophthalmoscopic procedure Following surgery a flat preparation was made and the distances between the retinal burns and the optic disc were determined directly

Materials and Methods

Patient data Our patient was a 55 year old seamstress with a five years history of progressive visual loss and proptosis on the right Neuroradiological examinations and neurosurgical exploration one year after the debut of symptoms showed that the cause was a spheno orbital meningioma with prominent bone reaction particularly in the roof and the lateral wall of the orbit The tumour was not resectable Intractable pain and excessive lacrimation drove the patient to demand enucleation four years later At that time the right eye was blind and protruded 6 mm relative to the left The lashes scratched against the spectacle lens on the right causing discomfort and soiling of the lens There was exotropia but free motility A few punctate lens opacities and minimal nuclear sclerosis did not hinder ophthalmoscopic evaluation The vitreous was fluid The optic disc was completely atrophic, and no vestige of a retinal nerve fibre layer could be seen The retinal vessels were narrow There were no signs of deformation of the bulb Retinoscopic refraction in cycloplegia was +4 0 sph the same as in the fellow eye

Photo coagulation Retinal markers were produced along the horizontal meridian of the retina prior to surgery employing a Carl Zeiss Photo Coagulator and a Fankhauser attachment Surface anaesthesia and a three mirror contact lens were used The burns were given a diameter of about one half optic disc diameter There was no bleeding

Perimetric angles The perimetric angles of the retinal markers were determined under cycloplegia in an apparatus built on the principle of monocular indirect ophthalmoscopy (Fig 1) Two hand ophthalmoscopes (Zeiss Jena) were used rigidly fixed to horizontal arms rotatable around a vertical axis Ophthalmoscopic lenses were fixed to the same arms and carefully aligned with the ophthalmoscopes appropriately placed cross hairs and the axis of rotation A protractor centered on the same axis allowed reading of the angular separation of the two sighting systems

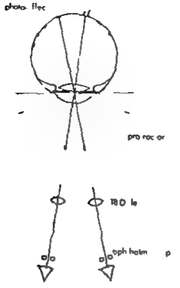


Fig 1
Scheme of apparatus used for determining perimetric eccentricity of retinal burns
Not to scale

The patient was carefully supported in a head rest The sighting apparatus was adjusted so as to make the axis of rotation coincide with the centre of the pupil A fixation light was provided in front of the seeing left eye

The two observers used one ophthalmoscopic set up each One was centered on the optic disc and the other was rotated along the vertical axis to bring the retinal markers into view and allow reading of their eccentricities relative to the optic disc

Retinal loci Immediately following enucleation the segment anterior to the ora serrata was removed Multiple cuts in the posterior segment allowed flattening of the horizontal strip against a plane cork slab Pins were used to hold the tissues in position A thin layer of vitreous fluid was left undisturbed There were no macroscopic suggestions of tension or wrinkling A graduated ruler was then superposed on the eye and the set up was photographed with diapositive colour film The ruler was then adjusted in position and new photographs were obtained This was repeated several times The whole procedure was finished in less than 20 min No shrinkage or drying was observed during this time

Results and Discussion

The photo coagulation markers were placed about 15 degrees apart four temporally and two nasally Inability to dilate the pupil fully prevented the placement of markers in the extreme periphery One week following photo coagulation the markers were white and easily identified ophthalmoscopically Their eccentricities were then determined Because of the less than maximal mydriasis each marker nearly completely filled the field of view in the sighting apparatus Although the limited field of view made it difficult to find the markers the same factor facilitated accurate alignment Five readings of the angular separations between the centres of markers and optic disc were obtained carefully adjusting the alignment of the apparatus prior to each reading The mean values and ranges of our readings are given in Table I Immediately following enucleation the anteroposterior and equatorial dia meters of the eye measured 24 and 23 5 mm respectively or slightly less than the average normal eye (Straatsma et al 1969)

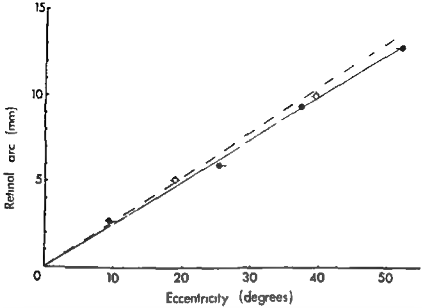
The positions of the markers were determined from photographs of the flat preparation selecting for measurement only those five photographs where the ruler lay closely parallel to the row of burns The centre to centre distances between markers and optic disc were read relative to the ruler image at 16 X The mean values and ranges of the five readings are given in Table I

For reasons of symmetry the optic axis is a more meaningful reference than the optic disc in establishing the relationship between eccentricity and retinal

Table I

Relationship between perimetric angle and retinal distance from optic disc Mean values and range ( )

Perimetric angle (degrees)	Retinal distance (millimetres)
Temporal retina	
19 5 (19 0–21 0)	5 3 (5 0– 5 5)
35 5 (35 0–36 5)	8 6 (8 5– 8 9)
49 5 (49 0–50 5)	12 6 (12 5–13 0)
62 0 (61 0–62 5)	15 4 (15 2–15 5)
Nasal retina	
9 0 (8 0–10 0)	2 5 (2 3– 2 8)
27 5 (27 0–28 0)	6 8 (6 5– 7 0)



Fig

Relationship between perimetric eccentricity and retinal arc referred to optic axis Open circles denote mean values of measurements in nasal hemiretina solid circles the same from the temporal side Ranges of observations are also indicated The solid line was fitted by eye The interrupted line represents the relationship derived by Drasdo & Fowler (1974)

arc Comparison of our results with those of previous theoretical calculations is also facilitated by such a translation of the data The improvisations necessitated by the clinical setting of this study hindered direct measurement of the position of the optic axis but it was estimated as follows From perimetric results obtained before the eye went blind the angular separation between the fovea and the centre of the optic disc was estimated to 15 degrees Noting that the eye was within normal limits of size it can be assumed that the angle between the line of sight and the optic axis approximates five degrees (Stine 1934 Duke Elder & Abrams 1970) Our eccentricity values therefore were translated 10 degrees subtracting on the temporal side of the eye and adding on the nasal side The retinal arcs were adjusted proportionally estimating the distance between the fovea and the optic disc centre to 3 9 mm The relationship relative to the optic axis between perimetric eccentricity and retinal arc is plotted in Fig 2 The closely linear relationship within the 0–50 degree range predicted from modern model eye studies (Drasdo & Fowler 1974 inlaid) appears well supported by our data although the line of best

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fit has a slightly smaller slope. The small difference in slope causes model eye estimates of retinal arc to err with no more than about 5 %. The slight discrepancy may well be due to preparation and measurement errors although optical and anatomical features of this particular eye or faults in model eye parameters are also possibilities. This cannot be decided until measurements have been obtained from additional eyes.

It is unfortunate that difficulties in dilating the pupil prevented us from obtaining more peripheral observations, as theoretical calculations predict a break down of the linear relationship outside about 50 degrees of eccentricity (Drasdo & Fowler 1974).

References

Duke-Elder S. & Abrams D. (1970) Ophthalmic optics and refraction. *System of Ophthalmology* Vol. 5, pp. 134–139. Kimpton, London.

Drasdo N. & Fowler C. W. (1974) Non-linear projection of the retinal image in a wide-angle schematic eye. *Brit. J. Ophthal.* 58, 709–714.

Frisen L. & Frisén M. (1976) A simple relationship between the probability distribution of visual acuity and the density of retinal output channels. *Acta ophthal. (Kbh.)* 54, 437–444.

Lotmar W. (1971) Theoretical eye model with aspherics. *J. opt. Soc. Amer.* 61, 1522–1529.

Stine G. H. (1934) Tables for accurate retinal localization. *Amer. J. Ophthal.* 17, 314–324.

Straatsma B. R., Landers M. B., Kreiger A. E. & Apt L. (1969) Topography of the adult human retina. In: Straatsma B. R., Hall M. O., Allen R. A. and Crescitelli F. Eds. *The retina. Morphology, function and clinical characteristics*, pp. 379–410. University of California Press, Berkeley and Los Angeles.

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ULTRASTRUCTURE AND DISTRIBUTION OF INTERCELLULAR JUNCTIONS IN CORNEAL ENDOTHELIUM

BY

OLE PETTER OTTERSEN and TORGEIR VEGGE

The intercellular junctions of the corneal endothelium has been studied in rabbit, monkey and human eyes. A union of apposing outer leaflet (tight junction) is usually found near the apical end of the intercellular clefts. However, evidence from lanthanum tracer studies indicates that the tight junctions do not seal the intercellular clefts completely. In addition to tight junctions, the presence of gap junctions or nexuses is demonstrated in all three species studied.

Key words: cornea – endothelium – intercellular junctions – ultrastructure

The corneal endothelium serves an important function in separating the aqueous humour from the corneal stroma. Its role is that of an active barrier, which to a certain extent controls the interchange of substance between the two compartments, and it is thus part of the barrier that surrounds the aqueous humour area. The nature of this endothelium is therefore important and has attracted much interest from physiologists as well as morphologists.

One important aspect is the patency of the intercellular clefts, since this influences the rate of diffusion of substances between the corneal stroma and the anterior chamber. Since Kaye et al. (1962) first described the ultrastructure of the corneal endothelium in the rabbit, several papers have appeared dealing with the detailed structure of the intercellular junctions of the endothelium

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Fig 1

Apical junctional zone in rabbit cornea Note several points of close approximation of cell membranes (arrows) some of which represent union of outer leaflets × 1?0 000

(Iwamoto & Smelser 1965 Hogan & Alvarado 1969 Kaye et al 1973 Leuenberger 1973) However there is still some disagreement concerning the exact morphological nature of these junctions

During the last decade much information has been collected on the function and morphology of intercellular junctions in general (for references see McNutt & Weinstein 1973)

The present paper is an attempt to clarify some ultrastructural details of the intercellular junctions of the corneal endothelium and to correlate this with current knowledge about junctions in general

Material and Methods

Both eyes from 7 albino rabbits were used The eyes were enucleated under Nembutal anaesthesia anterior segments were removed quartered and immediately immersed in cooled fixative The fixative was 1 5 % glutaraldehyde freshly made from 8 % stock under N in 0 1 M Na cacodylate buffer pH 7 4 with 0 025 % CaCl added For some specimens 0 7 % paraformaldehyde was added to the fixative while others were fixed directly in the osmium fixative All aldehyde fixed tissues were postosmicated with 1 % osmium in 0 16 M Na cacodylate buffer

In addition to this main material two human eyes and the eyes from three

Fig 2

Detail of junctional zone showing true union of outer leaflets (arrow) at the very apical end of intercellular cleft Rabbit cornea x 190 000

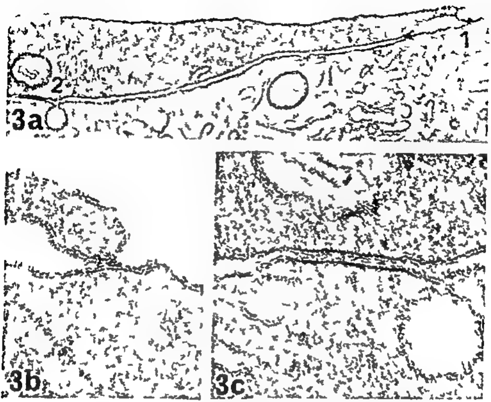

Fig 3

(a) Apical junctional zone in human cornea showing several points of close membrane approximation × 50 000 (b) Detail (junction 1) from (a) Note punctate tight junction. × 240 000 (c) Detail (junction 2) from (a) Note the intervening gap between apposed cell membranes typical of the nexus or gap junction × 240 000

vervet monkeys were studied These specimens were fixed by the above fixatives or by 2.5 % glutaraldehyde and 2 % paraformaldehyde in 0.1 M Na cacodylate buffer Dehydration was by alcohol or acetone and embedding material was either Araldite or TAAB embedding medium Samples from three rabbits and one monkey were treated with lanthanum according to Revel & Karnovsky (1967)

Some specimens were stained with uranyl *en bloc* Sectioning was done on LKB Ultrotomes sections were stained with uranyl or lead or both and examined in Siemens Elmiskop 1 or 1A

Results

Preservation of cytoplasmic detail as well as of cell membranes was good in all our samples The intercellular clefts of the corneal endothelium showed no dilations One to several intercellular junctions were found in each cleft in the sections and at least one of these junctions was found near the apical surface of the endothelium In this location a zone of junctions appeared to be present inasmuch as two to four close approximations of apposing cell membranes were nearly always found within a short apical segment of the cleft (Fig 1) Although we could only rarely define the exact structure of all such junctions at least one of them usually showed a union of outer leaflets (Figs 2 and 3 b) All such junctions had a very short apico basal extension Indeed they could best be described as points of union or punctate junctions This type of junction was found only in the apical part of the intercellular cleft

Very frequently another type of cell approximation was present in which the apposing cell membranes were separated by a narrow gap over a slightly longer segment of the cleft. The separating gap was about 20 Å and the extent along the cleft was up to one half of a micron (Fig 3 c) This is a so called gap junction or nexus (McNutt & Weinstein 1973) Up to 7 separate nexuses were found in each intercellular cleft They appeared in any part of the cleft ap

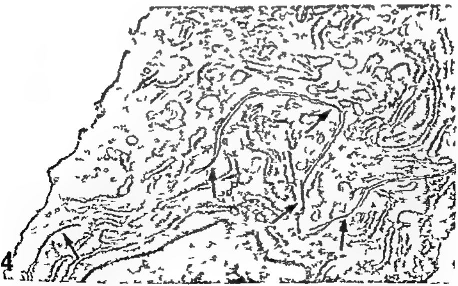

Fig 4

Survey electron micrograph showing example of nexus junction distribution along intercellular cleft (arrows) Rabbit cornea x 30 000

Fig 5

Peg and socket interdigitation with nexus junction (arrows) Rabbit cornea ×60 000

parently without preferential location (Fig 4) In many cases a nexus was found to form the interface between cells at the site of a rounded peg and socket junction (Fig 5)

In lanthanum treated specimens the endothelial cells invariably showed a lanthanum stained slightly fluffy material on their apical surface and the apical end of the intercellular clefts always showed a dense lanthanum deposit Sometimes successive pockets of the intercellular cleft within the junctional zone were filled with lanthanum the pockets apparently being formed by successive intercellular junctions (Fig 6)

Lanthanum never filled the intercellular clefts but scattered small granules of deposit could be found in any location within the cleft (Fig 7) confirming

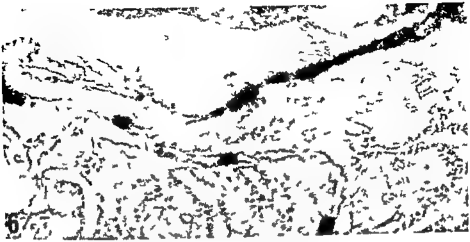

Fig 6

Apical junctional zone from lanthanum treated rabbit cornea Deposit in extreme apical end of intercellular cleft and in pockets within junctional zone ×80 000

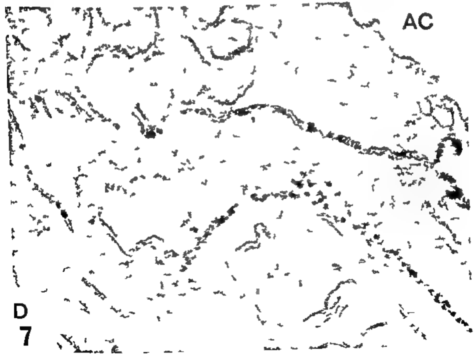

Fig 7

Granules of lanthanum deposit scattered along intercellular cleft of monkey corneal endothelium AC Anterior chamber D Descemet's membrane Osmium fixation unstained section ×45 000

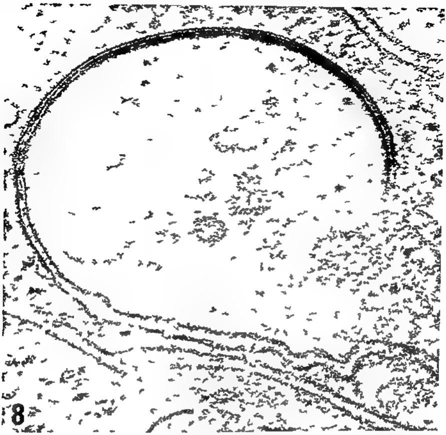

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Fig 8
Nexus from lanthanum treated monkey cornea Note lanthanum deposit in intervening gap × 160 000

the observations of Leuenberger (1973) and of Kaye et al (1973) In nexuses the intervening gap was frequently filled with lanthanum deposit (Fig 8)

Although we do not have comparable figures for the frequency of nexuses in the different species examined we believe that in this material there were more gap junction per cell in the rabbit than in the human

Discussion

Iwamoto & Smelser (1965) working with human material described a zonula occludens type of junction sealing the intercellular clefts of the corneal endo thelium Their observations were confirmed by Hogan & Alvarado (1969) Kaye and co workers had already shown that a junctional complex was always

present in this location (Kaye & Pappas 1962 Kaye et al 1962) although the importance of accurate definition of the junction was not known at that time

Working with colloidal lanthanum Leuenberger (1973) concluded that in the rat cornea the endothelial cells are connected only by so called gap junctions or nexuses Kaye et al (1973) found nexuses in rabbit corneal endothelium and showed that the intercellular clefts are penetrated by horseradish peroxidase both in the rabbit and in vervet monkeys

The present study corroborates the observation that in monkey and in rabbit colloidal lanthanum when added to the fixation medium reaches the inter endothelial clefts In terms of functional properties this requires that the inter cellular clefts are not sealed by a continuous zonula occludens (McNutt & Wein stein 1973) However we have definitely shown the presence of tight junctions in sections in all three species studied as previously demonstrated in human material by Iwamoto & Smelser (1965) and by Hogan & Alvarado (1969) We believe the only interpretation that is consistent with all the observations is that the corneal endothelial cells are girdled by incomplete zonulae occludentes It has been shown in other tissues that the extent and complexity of zonulae occludentes vary and that a labyrinthine passageway can sometimes be traced through the junctional zone (Friend & Gilula 1972)

In this manner large molecules may diffuse through what in cross sections appear to be a zonula occludens This has been suggested for the epithelium of the middle ear mucosa (Haye 1972 1973) and we believe that this is the explanation for the passage of colloidal lanthanum and horseradish peroxidase in the corneal endothelium One may speculate whether this type of junction is in a dynamic state allowing the leakiness of the corneal endothelium to vary with the functional state of the tissue Carefully designed experiments perhaps utilizing the freeze fracture technique to visualize intercellular junctions should be undertaken to resolve this point

The presence of gap junctions or nexuses in corneal endothelium has pre viously been demonstrated in rats (Leuenberger 1973) and in rabbits (Kaye et al 1973) In the present study it is shown that this type of junction is also present in monkeys and in the human Our observations indicate that the nexus here as in other epithelia occurs only in plaques and not in the form of zonules that encircle the cells In many epithelia this type of junction has been shown to act as a site of communication allowing the passage of relatively large molecules and ions from cell to cell (for references see McNutt & Weinstein 1973) We are not aware of any study on the function of the nexus in corneal endothelium However it would seem a reasonable speculation that it serves a similar func tion here We believe that careful physiological studies of this question would prove fruitful

References

Friend D [illegible] & Gilula N B (1972) Variations in tight and gap junctions in mammalian tissues *J Cell Biol 53* 758–776

Haye R (1972) Resorption of horseradish peroxidase from the middle ear cavity of guinea pigs *Z Zellforsch 123* 209–214

Haye R (1973) The epithelium of the middle ear in the guinea pig *Z Zellforsch 138* 283–294

Hogan M J & Alvarado J (1969) Ultrastructure of the deep corneolimbal region *Docum ophthal (Den Haag) 26* 9–30

Iwamoto T & Smelser G K (1965) Electron microscopy of the human corneal endothelium with reference to transport mechanisms *Invest Ophthal 4* 270–284

Kaye G I & Pappas G [illegible] (1962) Studies on the cornea I The fine structure of the rabbit cornea and the uptake and transport of colloidal particles by the cornea *in vivo J Cell Biol 12* 457–479

Kaye G I Pappas G D Donn A & Mallett N (1962) Studies on the cornea II The uptake and transport of colloidal particles by the living rabbit cornea *in vitro J Cell Biol 12* 481–501

Kaye G I Sibley R C & Hoefle F [illegible] (1973) Recent studies on the nature and function of the corneal endothelial barrier *Exp Eye Res 15* 585–613

Leuenberger P M (1973) Lanthanum hydroxide tracer studies on rat corneal endothelium *Exp Eye Res 15* 85–91

McNutt N S & Weinstein [illegible] S (1973) Membrane ultrastructure at mammalian intercellular junctions *Progr biophys molec biol 26* 47–101

Revel J P & Karnovsky M J (1967) Hexagonal array of subunits in intercellular junctions of the mouse heart and liver *J Cell Biol 33* C7–C12

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PHOTOGRAPHY OF THE NERVE FIBER LAYER IN RETINAL DISTURBANCES

BY

ANTTI VANNAS, CHRISTINA RAITTA and SEPPO LEMBERG

The diagnostic value of nerve fiber layer photography is assessed. The series comprised 39 patients with various neuro-ophthalmological diseases. Photography of the nerve fibers in the retina is time consuming and requires skill on the part of the photographer. Differences in the papillo-macular nerve fiber layer are difficult to distinguish using the present methods. The wasting of nerve fibers could be documented by photography in advanced cases with bitemporal hemianopia, but not in small relative scotomas. Cases with homonymous hemianopia are interesting because lesions in the optic tract can be differentiated from affections of the second neuron on the basis of retinal nerve fiber atrophy. In demyelinating diseases inspection of the retinal nerve fiber layer is of clinical importance and diagnostic changes appear.

Key words: demyelinating diseases – fundus photography – hemianopia – optic atrophy – retinal nerve fiber layer atrophy

At the beginning of this century Vogt (1913) made the observation that the nerve fiber layer in the retina could be observed by ophthalmoscopy. By using red free light he prevented the red reflexes from the choroid and sclera. This enabled him to follow nerve fiber bundles, but he could not decide whether this new *observation had any diagnostic value*.

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Years later Ito et al (1969) used enlarged fundus photographs to examine nerve fiber changes in optic neuritis Hoyt et al (1972 1973) laid down criteria for nerve fiber bundle defects and described several well documented cases with corresponding field defects Frisen & Hoyt (1973 1974) improved the photographic documentation of retinal details and described nerve fiber layer defects in multiple sclerosis In the Scandinavian literature Lundstrom (1974) published patients with local defects in the nerve fiber layer resulting from ischaemic optic neuropathy and increased blood pressure

This study was undertaken to determine the usefulness of photographic documentation of the retinal nerve fiber layer in lightly pigmented Finnish patients Special attention was paid to several macular lesions in order to discover whether corresponding nerve fiber layer defects could be seen

Materials and Methods

Our material comprised 39 patients from different age groups (Table I) Seven patients had only a unilateral central fundus lesion These patients were selected according to the pathological process to ensure that the corresponding papillomacular nerve fibers were destroyed The fellow eyes had good vision (0 8–1 0) and in the affected eyes vision was reduced to finger counting in all cases The remaining patients had a neuro ophthalmological disease Eleven patients had bitemporal hemianopia Nine patients had homonymous hemi

Table I
Age distribution of the patients

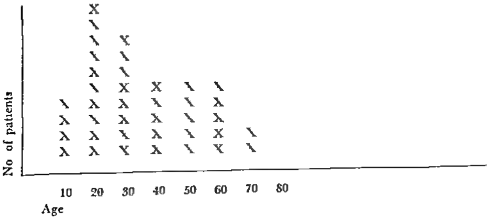

Fig 1

A toxoplasmic scar in the right macula No nerve fiber striations are visible in the right papillomacular (RE) area as compared with the unaffected left eye (LE)

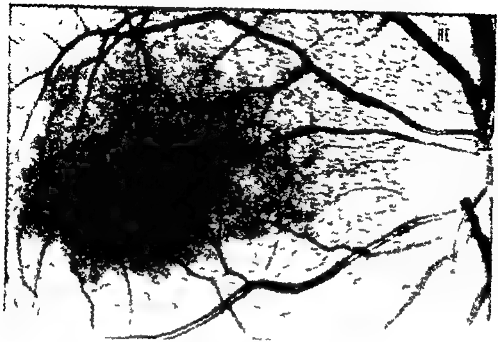

Fig 2 A and B

A man 39 years of age with left retinal artery thrombosis VA in RE 1 0 and LE FC 0 5 m The photographs (A) do not reveal differences in the papillomacular nerve fiber bundles The arcuate bundles (B) show wasting of the nerve fibers in LE (arrow)

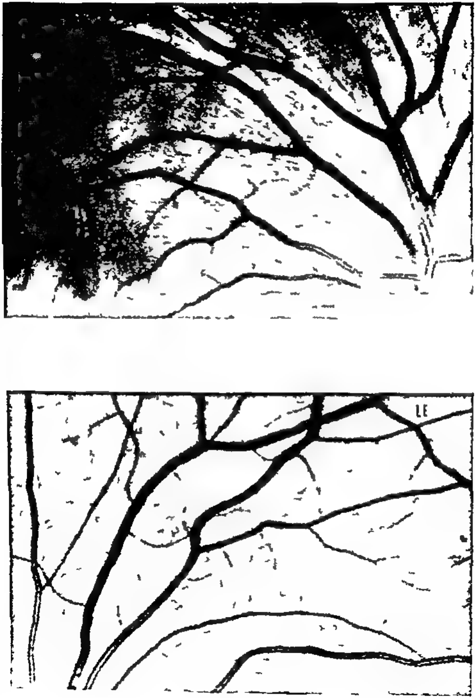

Fig. 2 B

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anopia This group also included patients with lesions behind the lateral geniculate body Twelve patients had a demyelinating process with visual disturbances All the patients were referred to our neuro ophthalmology unit

The fundus was examined through a dilated pupil using red free and regular bright light Careful notes and drawings were made and compared with the fundus photographs A Carl Zeiss camera with double enlargement was used for the photography A Kodak green filter (W 58) and plus X film were regularly used The films were developed and printed by standard laboratory techniques keeping in mind the weak contrast in fundus photographs

Results

Focusing was most important in the photography of retinal nerve fiber layer One half of the patients had to be rephotographed in spite of the fact that several exposures were taken of the same area

It seems to be very difficult to record changes in the papillomacular nerve fiber layer with our technique Finnish patients have blue eyes with little pigmentation and the contrast in the fundus is poor Degenerative changes in the outer retinal layers in older patients also decrease the contrast

Seven patients with unilateral macular disease were carefully studied for defects in the papillomacular nerve fiber bundle In all the cases the visual acuity in one eye was at least 0 8 while the contralateral eye could only see hand movements or count fingers Nerve fiber atrophy could be detected in only two patients with our technique These patients had almost no nerve fibers left in the papillomacular area and the reflex from the fundus was coarse (Fig 1) In five patients neither red free ophthalmoscopy nor fundus photography revealed detectable changes in the papillomacular area although some degree of nerve fiber atrophy was invariably present An example is a man of 39 years with thrombosis of the left central retinal artery Visual acuity in the affected eye was finger counting at 50 cm No changes were visible in the papillomacular bundles 7 months after the attack (Fig 2 A) The arcuate nerve fiber bundles showed definite atrophy in the affected left eye (Fig 2 B)

Eleven patients with bitemporal hemianopia were studied All of them were middle-aged and the nerve fiber layer could be seen in all the eyes No changes in the nerve fiber layer were seen in four patients These patients had only a slight quadrant defect in the upper temporal field The chiasmal compression had been released by earlier surgery and at the time of photography visual fields examination revealed relative scotomas In advanced cases with

absolute scotomas involving more than one quadrant in both temporal fields the photographic documentation of the nerve fibers corresponded with the field defects Nerve fiber layer documentation was of no special diagnostic use in this group

A nerve fiber defect was registered in 3 out of 9 patients with homonymous hemianopia Inspection of the retinal nerve fiber layer provided some diagnostic help in this group of patients when it was not known whether the lesion in the optic pathway was situated in front of or behind the lateral geniculate body

The inspection of retinal nerve fiber layer was most useful in demyelinating diseases As our material was collected from neuro ophthalmology files the diagnosis was already evident in most cases On re examination all the patients showed varying degrees of retinal nerve fiber layer atrophy and in some cases papillary pallor was also present For patients whose disease has not been diagnosed the method may be an important diagnostic aid A 20 year old man was admitted to our hospital because of poor vision For several months he had had visual disturbances especially after physical exercise On admission his visual acuity was FC in RE and 0 4 in LE In the RE he had a large

Fig 3

A male 20 years of age with multiple sclerosis The arcuate nerve fiber bundle shows diffuse atrophy and the vessels appear naked with a bright reflex (arrow)

central scotoma and the LE showed a relative central scotoma He had several slit like defects in his arcuate bundles (Fig 3) and a multifocal demyelinating process could be diagnosed Laboratory tests showed increased gammaglobulin and a pathological Mastix reaction in the spinal fluid

Discussion

Eye clinics usually possess the necessary equipment for fundus photography The same equipment can be used for nerve fiber layer documentation Our results however show that focusing is difficult and the amount of work needed in nerve fiber layer photography is many times in excess of that required for regular fundus photography Our pictures were taken by a professional eye photographer in the course of routine eye photography It is possible that the quality of the pictures might be improved with less re photographing if the photographer could devote himself entirely to nerve fiber layer documentation

Differences in the papillomacular nerve fiber layer were especially difficult to record although the amount of nerve fibers differed greatly from the contralteral eyes as shown by the visual acuity and previous pathological process The diameter of the nerve fibers in the papillomacular area is small and the atrophy of the fibers may be diffuse in contrast to the slit like atrophy that has been recorded in the arcuate bundles (Hoyt et al 1973 Frisen & Hoyt 1974) Furthermore the macular ring reflex was altered by retinal pigment epithelium changes in some eyes and could not be followed

Atrophy in the anterior visual pathways has mostly been graded for papillary pallor Our results indicate that a careful inspection of the retinal nerve fiber layer is helpful In bitemporal hemianopia a nerve fiber defect could be recorded if the visual field defect was absolute If the visual field defect was relative we could not detect changes in the nerve fibers with our methods

In homonymous hemianopia the lesion is most commonly behind the lateral geniculate body Three of our cases had a lesion anterior to the lateral geniculate body and nerve fiber atrophy was present in the fundus According to Lundstrom & Frisén (1975) the retrograde atrophy in the fundus appears 4–8 weeks after the trauma Thus careful ophthalmoscopy can aid the diagnosis if field tests cannot be performed or if the site of lesion has not been revealed beforehand

Our results concur with earlier reports (Frisen & Hoyt 1974) that nerve fiber layer inspection is of great value in demyelinating diseases One of our patients nicely demonstrated how ophthalmoscopy can confirm the presence of a multifocal demyelinating process during the initial examination

References

Frisen L & Hoyt W F (1973) Unsharp masking in fundus photography *Invest ophthal 12* 461–464

Frisen L & Hoyt W F (1974) Insidious atrophy of retinal nerve fibers in multiple sclerosis *Arch Ophthal (Chicago) 92* 91–97

Hoyt W F Frisén L & Newman N M (1973) Fundoscopy of nerve fiber layer defects in glaucoma *Invest ophthal 12* 814–829

Hoyt W F Schlicke B & Eckelhoff R J (1972) Fundoscopic appearance of a nerve fibre bundle defect *Brit J Ophthal 56* 577–583

Ito H Ozawa K Suga S & Mizuno K (1969) Red free light magnifying photography in neuritis and some retinal vascular lesions *Folia ophthal jap 20* 287–290

Lundstrom M (1974) Wasting of nerve fibers in the retina photographic documentation. *Acta ophthal (Kbh) 52* 842–850

Lundstrom M & Frisen L (1975) Evolution of descending optic atrophy *Acta ophthal (Kbh) 53* 738–746

Vogt A (1913) Herstellung eines gelbblauer Lichtfiltrates in welchem die Macula centralis in vivo in gelber Farbung erscheint, die Nervenfasen der Netzhaut und andere feine Einzelheiten derselben sichtbar werden und der Grad der Gelbfarbung der Linse ophthalmoskopisch nachweisbar ist *Albrect v Graefes Arch Ophthal 84* 293–311

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CONTRACTILE AND HISTOCHEMICAL PROPERTIES OF THE INFERIOR OBLIQUE MUSCLE IN THE RAT AND IN THE CAT

BY

JERKER HANSON and GUNNAR LENNERSTRAND

Mechanical and histochemical properties of inferior oblique muscles (IO) were compared in adult albino rat and pigmented cat The twitch contraction times and the fusion frequencies were about the same in both species indicating similar contractile properties of the fast contracting fibers Rat IO seemed to contain fewer slowly contracting fibers than cat IO half decay time of the twitch was shorter in rat than in cat muscles and fusion started at higher stimulus frequencies Fatigue resistance was lower in rat than in cat Post tetanic potentiation occurred in the cat but not in the rat IO
Almost all fibers of rat IO were rich in myofibrillar ATPase In cat IO most fibers showed high myofibrillar ATPase activity but some fibers in the global layer had moderate to small amounts of this enzyme This correlates well with the physiological differencies between cat and rat IO

Key words extra ocular muscle – cat – rat – physiology – histochemistry

Results of earlier studies indicate that cat and rat extraocular muscles have different mechanical properties (Close & Luff 1974) although they seem to consist of morphologically similar fiber types (Alvarado & van Horn 1975

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Asmussen et al 1971 Mayr 1975) In physiological experiments on the cat both fast and slow eye muscle fibers and motor units have been identified (Bach y Rita 1971 Lennerstrand 1974b Lennerstrand & Bach y Rita 1974) while in the rat only fast units have been found (Close & Luff 1974) Since it cannot be excluded that differences in experimental techniques might have accounted to some extent for these variations muscle properties in both species were investigated under identical (*in vivo*) conditions Moreover fatigue studies are lacking in rat eye muscles so it is not known if rat muscles are as fatigue resistant as cat extraocular muscles (Lennerstrand 1974b)

Previous work on skeletal muscle both in rat and cat has shown that there exists a close correlation of the histochemical staining patterns to the velocity of contraction and the resistance to fatigue of a muscle fiber (Burke et al 1973 Edstrom & Kugelberg 1968 Hanson 1974b Kugelberg 1973) Another object of the present study was to see if this relationship also holds in eye muscles

It has been possible to demonstrate that differences in functional properties between rat and cat inferior oblique (IO) muscles could be correlated mainly to the presence of fibers with low myofibrillar ATPase activity in cat eye muscles and the absence of such fibers in the rat muscles A preliminary report of some of these findings has been published elsewhere (Lennerstrand & Hanson 1975)

Methods

Adult albino rat (Sprague Dawley) and normally pigmented cat were anaesthetized with an ip or iv injection of pentobarbital (40 mg/kg b wt) Additional doses of anaesthetics were given iv The head was rigidly clamped and the IO muscle was prepared for stimulation and tension recording in the manner described by Bach y Rita & Ito (1966) The muscle was kept in warm mineral oil (35–37°C) in a pool formed by the raised nictitating membrane

Physiological studies

The motor nerve was placed over paired platinum wires of 0 25 mm diameter and stimulated with square wave pulses of 0 1 ms duration The pulses were delivered from a Grass S8 stimulator over a stimulus isolation unit Pulses of supramaximal intensity were used unless stated otherwise in the text For tension measurements the muscle tendon was attached to the anode peg of an RCA 5734 valve The signals were dc amplified and recorded on UV sensitive paper from the oscilloscope screen of a Medelec recording unit

The muscle was held isometrically at the length producing maximal twitch amplitude and the following mechanical parameters were determined

1) Twitch contraction time and half decay time

2) Apparent fusion frequency i e the lowest tetanic stimulus frequency to produce a smooth tension output

3) Degree of fusion of tension at low stimulus rates 0 5–50 Hz

4) Tetanic tension and rate of tension rise determined at stimulus frequencies from 50–800 Hz (Lennerstrand 1974a)

5) Endurance determined as the residual tension in per cent of the highest initial tension after 30 s of constant stimulation at 50 100 200 and 300 Hz

6) Post tetanic potentiation of the twitch response (amplitude contraction time and half decay time) caused by tetanizations of varying duration and stimulus frequency

In addition succinylcholine (Celocurin Vitrum) was injected iv in doses between 250 and 500 μg/kg b wt and the subsequent contracture recorded (Bach y Rita & Ito 1966) During the paralysis of the respiratory muscles caused by the drug the animals were ventilated by a pump

Twitch characteristics tetanic tension development and reactions to succinylcholine have previously been studied in cat IO muscles by Bach y Rita & Ito (1966) and Vilis (1973) Our results were found to be consistent with theirs with respect to these parameters Therefore only a few experiments were considered necessary for the study of endurance and post tetanic potentiation

Histochemical studies

When tension recordings were completed the muscles were removed and immediately frozen Sections cut in a cryostat were stained for

1) ATPase after pre incubation according to Brooke & Kaiser (1969) at pH 9 4 and subsequent incubation according to Pearse (1960) after Padykula & Herman (1955) ATPase concentration 1 52 mg/ml

2) ATPase after pre incubation at pH 4 35 (Brooke & Kaiser 1970) subsequent incubations as in 1)

3) ATPase after pre fixation with formaldehyde (Hayashi & Freiman 1966) subsequent incubation as in 1)

4) Succinic dehydrogenase (SDH Nachlas et al 1957 cf Pearse 1960) and

5) Lipids (Sudan black B Carleton & Drury 1957)

Fiber counts were performed on microphotographs

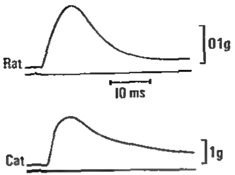

Fig 1
Twitch responses of rat and cat IO muscles

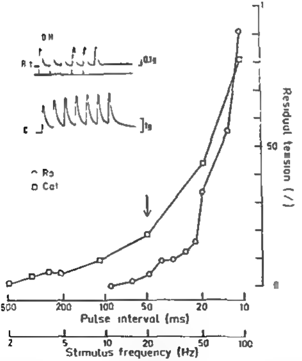

Fig 2
Partial fusion of twitches in rat and cat IO at repetitive stimulation of low frequencies The residual tension of the first twitch at the time for the start of the second twitch has been plotted against stimulus interval (upper scale) and stimulus frequency (lower scale) The inset shows the responses of rat IO (top traces) and cat IO (bottom trace) to stimulation at about 90 Hz These values of partial fusion are shown by the arrow

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in inset of Fig 2 stimulation at 20 Hz gave barely overlapping twitches in the rat while in the cat considerable summation had already occurred This is shown in a diagrammatic form in Fig 2 for stimulus frequencies between 10 and 100 Hz in the rat and between 2 and 100 Hz in the cat

Endurance Muscle fatigue was more marked in rat than in cat eye muscles After constant stimulation for about 30 s at 100 and 200 Hz (Fig 3) the remaining tension in per cent of the initial peak tension was about twice as high in the cat as in the rat (Table I)

Fatigue was also determined at the intensity of single pulse nerve stimulation that produced half the maximal twitch amplitude The endurance values obtained in this manner did not differ from those found in the experiments with supramaximal stimulation in either the cat or the rat

Effect of succinylcholine (Sch) In both rat and cat eye muscles i v injection of Sch produced a contracture of 3 to 5 min duration The amplitude of this contracture was measured at the point of the curve where the twitch response to nerve stimulation had vanished indicating complete neuromuscular block The amplitude was about 1/3 of the total tetanic tension (Table I) Similar values have been obtained for Sch contractures in the cat by Bach y Rita & Ito (1966)

Table I
Isometric characteristics of rat and cat IO muscles

	Rat			Cat		
	Mean	Range	No obs	Mean	Range	No obs
Twitch						
Contraction time (ms)	7 8	6 4–8 5	8	6 3	5 6–8 1	4
Half decay time (ms)	7 0	5 4–8 [illegible]	8	12 4	10 7–15 5	4
Tetanus						
Apparent fusion frequency (Hz)	313	[illegible]50–350	8	346	[illegible]	4
Endurance at 200 Hz (%)	10	[illegible]	8	27	2[illegible]–30	4
Succinylcholine effect (% of max tetanic tension)	31	16–[illegible]3	5	27	20–34	4

Post tetanic potentiation (PTP) The twitch amplitude was recorded at low sweep speed within 1–2 s after a 30 s stimulation and compared with values obtained immediately before the tetanus (Fig 3) In the rat an average decrease in amplitude of 22 % (range 0–40 % n = 5) was seen after stimulation at 200 Hz for 30 s whereas in the cat there was an average increase of 53 % (range 30–80 % n = 4) Shorter periods of stimulation with less fatigue of the twitch response did not produce any PTP in rat eye muscle

Contraction curves at fast sweep speed 25 60 s after the end of the 30 s tetanus were studied (Fig 4) In 8 rat muscles only minor changes (about 10 %) were seen in the time course of the twitch In the cat no changes in the contraction time were seen However there was always an increase in the half decay time sometimes quite marked (up to 200 %) especially after high frequency stimulation (200–300 Hz) The effect on the amplitude and the decay time of the twitch subsided almost entirely within 2 min

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The grouping of fibers with large ones located on the inner or *global* side of the muscle and small fibers on the outer *orbital* side (Alvarado & van Horn 1975 Mayr 1971) was less distinct in the rat than in the cat muscles (Fig 5) Areas between the main layers contained many fibers of intermediate size

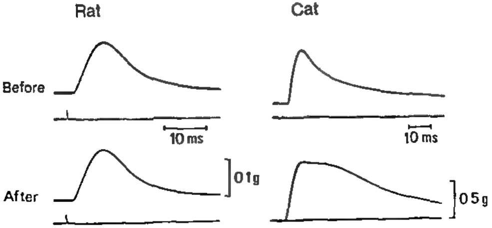

Fig 4
Effects of a stimulation at 200 Hz for 30 s on the twitch contraction curves of IO muscles from rat and cat

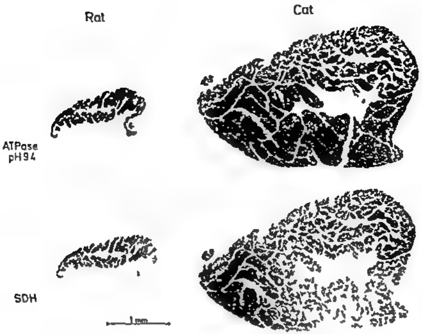

Fig 5
Transverse sections of whole IO muscles from rat and from cat stained for myofibrillar ATPase at pH 9.4 and for SDH

Rat muscles (Figs 6 and 7 left rows)

The vast majority of the fibers showed high or very high intensity of staining for myofibrillar ATPase at pH 9.4 Pre fixation in formaldehyde revealed slight variations between the fibers After pre incubation at pH 4.35 most fibers stained lightly However 20–40 % of the fibers were darker than the rest and were classified as group IIC fibers according to Brooke & Kaiser (1970)

All the rat muscle fibers had high or very high SDH activity and lipid content

Cat muscles

Global layer (Fig 6 right row) Of the fibers in the global layer about 20 % stained less intensely than the rest for myofibrillar ATPase at pH 9.4 After pre fixation with formaldehyde this difference in staining intensity became more prominent Slight variations in intensity were also seen between the fibers which stained darkly at pH 9.4 Pre incubation at pH 4.35 gave essen

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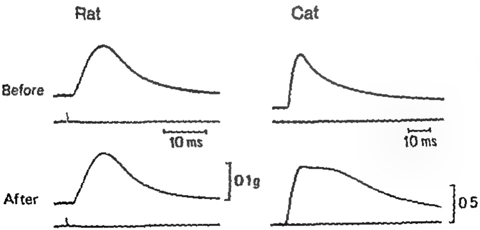

Fig 4
Effects of a stimulation at 200 Hz for 30 s on the twitch contraction curves of 10 muscles from rat and cat

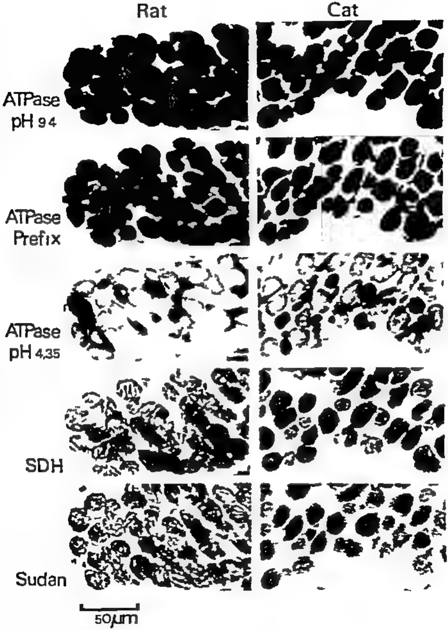

Fig ¯

Micrographs from areas with small muscle fibers (orbital layer) of rat and cat IO
Serial sections stained as in Fig ■

tially a reversal of the staining pattern seen after pre fixation with formal dehyde

Intermediate SDH activity was seen in the fibers which stained lightly for ATPase at pH 9 4 and after pre incubation with formaldehyde Fibers with high myofibrillar ATPase activity had high intermediate or low SDH activity The lipid content usually paralleled the SDH activity

Orbital layer (Fig 7 right row) All the fibers stained intensely for myo fibrillar ATPase both at pH 9 4 and after pre incubation with formaldehyde After pre incubation at pH 4 35 about 10 % of the fibers stained darkly about 80 % stained moderately and only 10 % of the fibers stained lightly

The SDH activity was high or very high in all the fibers except in some of the fibers staining heavily for ATPase at pH 4 35 The lipid content of the fibers largely followed the SDH activity

Discussion

The physiological properties of rat and cat eye muscle vary with respect to both twitch and fatigue characteristics and these differences seem to be com patible with variations between species in muscle fiber histochemistry

Speed of contraction The physiological data on twitch contraction imply that the rat inferior oblique muscle is composed of a fairly uniform population of predominantly fast contracting fibers (see also Close & Luff 1974) In cat eye muscle an additional slow fiber component could be distinguished signified by the longer decay time of the twitch

Tetanic stimulation data indicate that the fast fibers of both rat and cat have similar contractile properties The frequencies of stimulation needed to produce a total fusion of tension were similar and the rate of tension rise varied in the same manner with stimulation frequency in both animals The prominent slow component in cat eye muscle was revealed by the much lower stimulus frequency needed to induce partial fusion in cat than in rat

Investigations on rat and cat skeletal muscles have shown that there is a close correlation between the speed of contraction and the myofibrillar ATPase activity in a muscle fiber (Burke et al 1973 Hanson 1974b Kugelberg 1973) the more ATPase the faster the contractions In the rat practically all fibers were rich in ATPase but in the cat a small but significant fraction of the fibers had a lower ATPase content The latter would then be the slowly con tracting fibers found by physiological tests to be much more abundant in cat than in rat eye muscle

In both rat and cat eye muscles fibers were seen that stained darkly for ATPase at pH 9 4 as well as at pH 4 35 These fibers were usually located in the orbital regions and were classified as group IIC fibers (Brooke & Kaiser 1970) They have been considered an undifferentiated precursor to IIA and IIB fibers (Brooke et al 1971) or representing a transitional form between slow and fast muscle fibers of intermediate contraction speed (Kugelberg 1973) Such fibers have previously been identified in the muscle spindles (Yellin 1969) The intrafusal fibers are known to be multiple innervated (Barker et al 1970) This is also the case for part of the orbital layer fibers (Alvarado & van Horn 1975 Mayr 1971) It is possible that possession of both alkali and acid stable ATPase is a characteristic of multiply innervated fibers However the multiply innervated fibers which are fairly rich in ATPase must be similar to those found in avian muscles (Asmussen et al 1969) with relatively high contraction velocity (Ginsborg 1960) These fibers cannot be the type of multiply innervated muscle fibers found in amphibia which almost lack ATPase (Smith & Ovalle 1973 H Nystrom personal communication) and which contract at an extremely low velocity (Lannergren & Smith 1966)

Endurance to long activations When exposed to a continuous activation of 30 s duration rat eye muscles fatigued more easily than cat eye muscles al though much less than other fast rat muscles (Edstrom & Kugelberg 1968) The rates of stimulation applied were within the range of steady state firing rates of eye motor units in the alert animal (see Lennerstrand 1974b)

When skeletal muscle fibers of equal levels of ATPase are compared the amount of succinic dehydrogenase (SDH) an oxidative mitochondrial enzyme parallels the fatigue resistance of the fibers but slow fibers with low ATPase content may show better fatigue resistance even with moderate amounts of SDH than fast fibers rich in SDH (Kugelberg 1973) It seems likely therefore that the species variation that has been observed with respect to fatigue of eye muscles is also related to the higher proportion of slowly contracting fibers in the cat than in the rat

Effect of succinylcholine (Sch) The relative amplitudes of Sch induced con tractures were identical in both species It has been suggested that the con tracture results from a long lasting depolarization of multi innervated fibers the focally innervated fibers instead being flaccidly paralysed by the drug (Bach y Rita 1971) Recently the Sch depolarized fibers in cat eye muscles have been morphologically identified they were shown to be of the multi innervated type (Nichols et al 1974) It might therefore be suggested that the amplitude of the contracture in relation to the total tension that can be produced will give an estimate on the proportion of multiply innervated fibers in an eye muscle The relative amount of multi innervated fibers would be similar in rat and cat eye muscles which is also supported by morphological findings (Alvarado & van Horn 1975 Mayr 1971)

Post tetanic potentiation (PTP) No trace of PTP was seen in the rat IO muscles after any of the stimulation sequences applied In other fast rat muscles the twitch amplitude is augmented by up to 250% after 10 Hz stimulation for 15 s (Hanson 1974a b) No explanation for this difference is offered at present In the cat IO muscles a moderate increase in the amplitude and a marked increase in the decay time of the twitch was seen after stimulation at high frequencies PTP appearing after high frequency tetanization in cat soleus muscles is due to repetitive discharge (Bowman et al 1962 Feng et al 1939 Nystrom 1968 Olson & Swett 1971 Standaert 1964) Repetitive discharge in the slowly contracting muscle fibers of the cat inferior oblique muscle might explain the potentiation observed If so the degree of PTP evoked by high frequency stimulation would be an indicator of the amount of slowly contracting fibers in the muscle

Functional implications It may be speculated that the existence of a slow fiber component in cat eye muscle and its almost complete absence in rat eye muscles could be related to the state of binocular vision in the two species The cat frontally directed eyes possesses a high degree of binocular single vision The albino rat on the other hand would largely lack binocularity because of its laterally placed eyes and also because of the abnormalities of the central visual pathways that are known to exist in albinos of different species (Guillery et al 1973) Binocular single vision requires fusional (vergence) eye movements which are of a sluggish tonic type It could be that the slow motor component has been better developed in the cat partly to subserve this type of eye motor control On the other hand eye muscles in sheep have fibers with low ATPase activity (Harker 1972) likely to contract slowly although sheep have only a limited binocular visual field and probably a poorly developed system for vergence movements It is possible therefore that the variations between rat and cat with regard to eye muscle fiber composition would merely reflect the differences in size and weight of the eyes Further experimentation in animals of the same species with and without defects of binocular vision could clarify this problem

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References

Alvarado J & van Horn C 1975) Muscle cell types of the cat inferior oblique In Lennerstrand G and Bach y Rita P Eds *Basic Mechanisms of Ocular Motility and Their Clinical Implications* pp 15–43 Pergamon Press Oxford

Asmussen G Kiessling A & Wohlrab F (1969) Histochemische differenzierbare Sorten von Muskelfasern in M latissimus dorsi des Huhnes *Experientia (Basel)* 25 959–961

Asmussen G Kiessling A & Wohlrab F (1971) Histochemische Charakterisierung der verschiedenen Muskelfasertypen in den ausseren Augenmuskeln von Saugetieren *Acta anat (Basel)* 79 526–545

Bach y Rita P (1971) Neurophysiology of eye movements In Bach y Rita P Collins C C and Hyde J E Eds *The Control of Eye Movements* pp 7–45 Academic Press New York

Bach y Rita P & Ito F (1966) In vivo studies on fast and slow fibers in cat extra ocular muscles *J gen Physiol* 49 1177–1198

Barker D Stacey M C & Adal M N (1970) Fusimotor innervation in the cat *Proc roy Soc B* 258 315–346

Barmack N H Bell C C & Rence B G (1971) Tension and rate of tension development during isometric response of extraocular muscle *J Neurophysiol* 34 1072–1079

Bowman W C Golberg A A J & Raper C (1962) A comparison between the effects of a tetanus and the effects of sympathomimetic amines of fast and slow contracting mammalian muscle *Brit J Pharmacol* 19 464–484

Brooke M H & Kaiser K K (1969) Some comments on the histochemical characterization of muscle adenosine triphosphatase *J Histochem Cytochem* 17 431–432

Brooke M H & Kaiser K K (1970) Muscle fibre types How many and what kind? *Arch Neurol Psychiat (Chic)* 23 369–379

Brooke M H Williamson E & Kaiser K K (1971) The behavior of four fiber types in developing and reinnervated muscle *Arch Neurol Psychiat (Chic)* 25 360–366

Burke R E Levine D N Tsairis P & Zajac III F E (1973) Physiological types and histochemical profiles in motor units of the cat gastrocnemius *J Physiol (Lond)* 234 723–748

Carleton H M & Drury R A B (1957) *Histological Technique* 3rd ed Oxford University Press London

Close R I & Luff A R (1974) Dynamic properties of inferior rectus muscle of the rat *J Physiol (Lond)* 236 259–270

Edstrom L & Kugelberg E (1968) Histochemical composition, distribution of fibres and fatiguability of single motor units *J Neurol Neurosurg Psychiat* 31 424–433

Feng T P Li T H & Ting Y C (1939) Studies on the neuromuscular junction XII Repetitive discharges and inhibitory after effect in post tetanically facilitated responses of cat muscles to single nerve volleys *Chin J Physiol* 14 55–80

Ginsborg B L (1960) Some properties of avian skeletal muscle fibres with multiple neuromuscular junctions *J Physiol (Lond)* 154 582–598

Guillery R W Scott G L Cattanach B M & Deol M S (1973) Genetic mechanisms determining the central visual pathways of mice *Science* 179 1014–1016

Hanson J (1974a) The effects of repetitive stimulation on the action potential and the twitch of rat muscle *Acta physiol scand* 90 387–400

Hanson J (1974b) Effects of repetitive stimulation on membrane potentials and twitch in human and rat intercostal muscles *Acta physiol scand* 92 238–248

Harker D W (1972) The structure and innervation of sheep superior rectus and levator palpebrae extraocular muscle I Extrafusal muscle fibres *Invest Ophthal 11* 956–969

Hayashi M & Freiman D G (1966) An improved method of fixation for formalin sensitive enzymes with special reference to myosin adenosine triphosphatase *J Histochem Cytochem 14* 577–581

Kugelberg E (1973) Histochemical composition contraction speed and fatiguability of rat soleus motor units *J Neurol Sci 20* 177–198

Lannergren J & Smith R S (1966) Types of muscle fibres in toad skeletal muscle *Acta physiol scand 68* 263–274

Lennerstrand G (1974a) Mechanical studies on the retractor bulbi muscle and its motor units in the cat *J Physiol (Lond) 236* 43–55

Lennerstrand G (1974b) Electrical activity and isometric tension in motor units of the cat s inferior oblique muscle *Acta physiol scand 91* 458–474

Lennerstrand G & Bach y Rita P (1974) Activation of slow motor units by threshold stimulation of cat eye muscle nerves *Invest Ophthal 13* 879–882

Lennerstrand G & Hanson J (1975) Physiological and histochemical characteristics of rat and cat extraocular muscle *J EEG Clin Neurophysiol 39* 101I

Mayr R (1971) Structure and distribution of fibre types in the external eye muscles of the rat *Tissue & Cell 3* 433–462

Mayr R (1975) Discussion remarks In Lennerstrand G and Bach y Rita P Eds *Basic Mechanism of Ocular Motility and Their Clinical Implications* pp 43–45 Pergamon Press Oxford

Nachlas M M Tsou K C de Souza E Cheng C S & Seligman A M (1957) Cytochemical demonstration of succinic dehydrogenase by the use of new p nitrophenyl substituted ditetrazole *J Histochem Cytochem 5* 420–436

Nichols K Bach y Rita P Lennerstrand G & Alvarado J (1974) Morphology of extraocular muscle fibers depolarized by succinylcholine *J Ultrastruct Res 48* 169

Nystrom B (1968) Mechanical and electrical responses to single shocks in developing cat leg muscles following tetanization *Acta physiol scand 74* 207–225

Olson C & Swett C P (1971) Effect of prior activity on properties of different types of motor units *J Neurophysiol 34* 1–16

Padykula H A & Herman E (1955) The specificity of the histochemical method for adenosine triphosphatase *J Histochem Cytochem 3* 170–183

Pearse A G E (1960) *Histochemistry Theoretical and Applied* 2nd ed J & A Churchill London

Smith R & Ovalle Jr W K (1973) Varieties of fast and slow extrafusal muscle fibres in amphibian hind limb muscles *J Anat (Lond) 116* 1–24

Standaert F G (1964) The mechanism of post tetanic potentiation in cat soleus and gastrocnemius muscles *J gen Physiol 47* 987–1101

Vilis T (1973) Mechanical properties of the extraocular muscles of the cat Ph D Thesis McGill University Montreal

Yellin D (1969) Unique intrafusal and extraocular muscle fibres exhibiting dual actomyosin ATPase activity *Exp Neurol 25* 153–163

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OCULAR FUNCTION IN CIRRHOSIS OF THE LIVER

BY

ERIK KROGH and HELMER RING LARSEN

The ocular state of 28 ascertained non alcoholic females with cirrhosis of the liver was assessed Only twenty were able to go through the complete colour vision test, and among these, three patients (one without and two with increased level of serum bilirubin) with acquired colour vision defects were observed Visual acuity visual field intraocular pressure binocular function slit lamp microscopy ophthalmoscopy and tear production were normal in all cases It is concluded that the frequency of colour vision defects in the present sample is increased and that alcohol abuse is not a prerequisite for colour vision defects in patients with cirrhosis

Key words cirrhosis of the liver – colour vision – acquired colour vision defects – tritanomalia – ophthalmia hepatica

In earlier ophthalmological literature the term *ophthalmia hepatica* was used for signs and symptoms of ocular dysfunction in patients with prolonged disease of the liver Amblyopia hemeralopia and concentric diminution of the visual field as well as xerosis of the conjunctiva blurring of the optic disc and pigmentary degeneration of the retina were seen (Baas 1894 Hori 1895 Hartshorne 1934) Pigmentary changes and choroidal exudation and infiltration were observed in dogs following ligation of the common bile duct (Dolganoff 1897) However the information does not allow a decision to be

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Table 1

...al biochemical data Farnsworth 28 and Farnsworth 100 colour vision test scores in patients with non alcoholic cirrhosis

Case	...	Diagnosis	Serum albumin µmol/l (532–813)	Pro thrombin time (95–115)	Serum bilirubin µmol/l (2–17)	GO trans aminases µ/l (5–25)	F 28 score*	F 100 score**
		Idiopathic cirrhosis	563	61	22	56	–	–
		Idiopathic cirrhosis	624	[illegible]0	8	33	–	–
		Idiopathic cirrhosis	3[illegible]2	84	45	51	–	–
		Idiopathic cirrhosis	[illegible]61	95	4	9	–	–
		Idiopathic cirrhosis	467	69	22	21	–	–
		Primary biliary cirrhosis	411	98	95	77	–	–
		Idiopathic cirrhosis	347	25	29	26	–	–
		Lupoid cirrhosis	446	54	9	13	–	–
[illegible]	FJ	Idiopathic cirrhosis	540	98	9	7	5	156
	JF	Primary biliary cirrhosis	711	119	6	64	0	16
[illegible]	HE	Idiopathic cirrhosis	615	89	10	57	0	4
[illegible]	RO	Primary biliary cirrhosis	4[illegible]9	109	7	16	0	64

13	18	EP	Idiopathic cirrhosis	544	59	37	260	0	8
14	54	AR	Primary biliary cirrhosis	427	79	106	73	0	60
15	54	IF	Primary biliary cirrhosis	319	130	92	70	0	24
16	73	IN	Primary biliary cirrhosis	443	190	16	45	0	24
17	53	BE	Primary biliary cirrhosis	501	157	96	115	0	16
18	70	HV	Primary biliary cirrhosis	368	96	286	63	1	160
19	56	ES	Primary biliary cirrhosis	4 0	101	79	90	4	112
20	31	LA	Primary biliary cirrhosis	562	130	11	56	1	44
21	48	EA	Primary biliary cirrhosis	464	89	10	19	1	72
22	67	EL	Primary biliary cirrhosis	418	108	30	130	2	48
23	48	EP	Idiopathic cirrhosis	361	47	39	46	0	52
24	75	AO	Idiopathic cirrhosis	435	73	21	52	0	36
25	77	LH	Idiopathic cirrhosis	433	71	17	45	2	72
26	79	AI	Idiopathic cirrhosis	539	97	8	67	2	64
27	49	MC	Primary biliary cirrhosis	456	115	15	140	1	56
28	17	BC	Lupoid cirrhosis	569	90	15	230	0	72

* *The interchange of one or two pairs of adjacent chips was considered normal* In this material patients Nos 9 and 19 were situated above this level

** A value of 128 or more was interpreted as a pathological hue discrimination

reached as to whether this variegated pathology depends on the diseased function on the liver *per se* on common aetiological factors (congenital lues chronic alcoholism) or on non specific conditions such as general malnutrition and vitamin deficiencies (especially of A and K)

In recent years a number of reports have indicated an apparently increased *frequency of colour vision defects (CVD) in patients with alcoholic cirrhosis* of the liver Cruz Coke (1965a b 1972) put forward a theory on genetic linkage between alcoholic cirrhosis and CVD of a predominantly red green type whereas Fialkow et al (1966) and Smith & Brinton (1971) demonstrated reversible CVD in alcoholics submitted to treatment In the latter sample no signs of pathological liver function were present and it is well known that alcohol induced optic neuritis is accompanied by CVD (Saraux et al 1966) Klein et al (1972 1974) found CVD of the acquired type in association with chronic liver disease but the alcohol consumption of the patients was not explored

The purpose of the present study has been to investigate various ophthalmological parameters in patients with cirrhosis of the liver on a sufficient diet and with no or only small and occasional alcohol consumption Particular emphasis has been given to the colour vision state whereas testing of dark adaptation was omitted because a few trials showed that the test period could be unduly long for these patients Besides a reduced dark adaptation capacity among cirrhotic patients has been demonstrated in earlier literature in connexion with decreased serum levels of vitamin A (Klein et al 1974)

Material

Twenty eight females with bioptically verified cirrhosis of the liver were examined Males were excluded because of the appreciable risk of genetical CVD Only 20 (Nos 9–28) were able to go through the complete colour vision test schedule without signs of mental fatigue This selection was not desired but was necessary In order to evaluate the normal variability 20 normal females of a similar age span were also examined for CVD Some biochemical data representing the hepatic function of the patients are shown in Table I

Methods

The ophthalmological examination included determination of visual acuity visual field (5/1000 white isopter) intraocular pressure (Goldmann s applanation tonometer) binocular state (cover test Maddox wing and rod *Titmus*

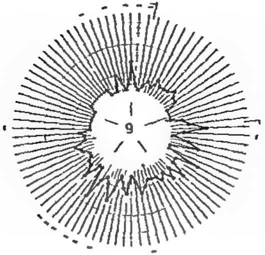
pictures for stereoscopic vision) followed by slit lamp microscopy and ophthalmoscopy Tear production was examined with Schirmer s test, and vital staining with a mixture of rose bengal and sodium fluoresceinate was also performed Colour vision was tested with Ishihara pseudoisochromatic plates the Nagel anomaloscope the Farnsworth 28 hue test and the Farnsworth 100 hue test In evaluation of the F 28 test the interchange of one or two pairs of adjacent chips was considered normal For the F 100 test Farnsworth (1957) considered a total error score of 100 or more to give evidence of a pathological discrimination Verriest (1963) discovered that the age and sex of the test persons influenced the score As the age span of the present sample is larger than that of Verriest s the mean ± 2 S D of the female part of his sample (= 127) is taken as another guiding figure

Results

Apart from the colour vision tests the ophthalmological examination of the patients gave completely normal findings Three patients (Nos 9 18 and 19) read the Ishihara plates without faults and produced normal anomaloscope *settings but differed from the rest of the sample when examined using either* the F 28 test the F 100 test or both Table I and Fig 1 summarize these findings which point towards a CVD of the acquired type The suggested bipolar patterns of patients Nos 18 and 19 approximating to a tritan defect do not contradict this statement since a genetic origin for such defects is highly doubtful (Ferguson 1972) The examination of the three patients was repeated after two weeks with no significant change They also had normal levels of serum vitamin A and consequently a reversible CVD due to vitamin A deficiency can be excluded (Bronte Stewart & Foulds 1972) The F 100 error score range of the normal sample was 4–60 and similar normal results were found with the other colour vision tests

Discussion

The outcome of the present investigation suggests that the signs and symptoms listed under the heading *ophthalmia hepatica* are only secondarily related to chronic disease of the liver On the other hand the 3/20 subjects with acquired CVD signifies a much higher frequency than is found in unselected samples (François et al 1957 chi square test $P < 0.0001$) According to the data of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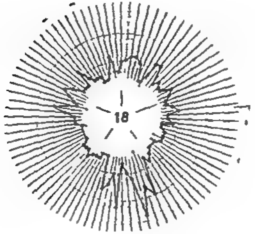
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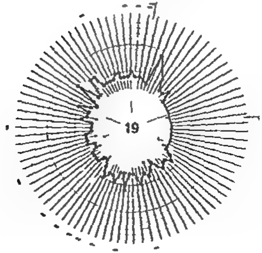
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Verriest (1963) the outcome of the F 100 test in patient No 19 should be interpreted with caution However the pathological outcome of the F 28 test and the absence of any visible pre receptorial explanation (yellowing of the lens) justifies classification of the patient as a colour defective

Two of the patients with CVD had high serum bilirubin levels (Table I) and it is conceivable that this would influence colour perception The intra ocular bilirubin content in icteric patients is however negligible (Toews & Basu 1962) but an investigation of highly icteric patients with recent occlu sion of the bile duct would be a valuable supplement to the present study

In contrast to earlier studies of CVD in cirrhotic patients the present sample consists of ascertained non alcoholic patients in good dietary condition Conse quently alcoholism and/or malnutrition are not prerequisites for CVD in con nexion with this disease An estimate of the prevalence of CVD in the cirrhotic population based on the present small sample would not be justified However it might well be high since these types of CVD usually pass unnoticed by the patient and the authorities On the other hand they are too unspecific to serve as a diagnostic criterion of cirrhosis of the liver

References

Baas K L (1894) Ueber eine Ophthalmia hepatitica *Albrecht v Graefes Arch Ophthal 40 (5)* 212–246

Bronte Stewart J & Foulds W S (1972) Acquired dyschromatpsia in vitamin A de ficiency *Mod Probl Ophthal 11* 168–173

Cruz Coke R (1965a) Colour blindness and cirrhosis of the liver *Lancet 2* 1131–1133

Cruz Coke R (1965b) Colour blindness and alcohol addiction *Lancet 2* 1348

Cruz Coke R (1972) Defective color vision and alcoholism *Mod Probl Ophthal 11* 174–127

Dolganoff W (1897) Ueber die Veranderungen des Auges nach Ligatur des Gallen blase *Arch Augenheilk 34* 196–220

Farnsworth D (1957) *The Farnsworth Munsell 100 hue test for the examination of color discrimination Revised manual* Munsell Color Co Baltimore

Ferguson W J W (1972) Anomalies of light sense and of colour sense In Sorsby A Ed *Modern Ophthalmology Vol 3* pp 189–197 Butterworth London

Fialkow P J Thuline H C & Fenster L F (1966) Lack of association between cirrhosis and the common types of color blindness *New Engl J Med 275* 584–587

Fig 1

The Farnsworth 100 hue test charts for patients Nos 9 18 and 19 The total error scores are 156 160 and 119 respectively The distribution of errors is diffuse in patient No 9 diffuse with a large hump in the blue green region in No 18 and shows a bipolar pattern compatible with tritanomalia in No 19

François J Verriest G Mortier V & Vanderdonck R (1957) De la frequence des dyschromatopsies congenitales chez l homme *Ann Oculist (Paris) 190* 5–16
Hartshorne W (1934) A case of choroidal atrophy without night blindness *Amer J Ophthal 17* 945–948
Hori (1895) Zur Anatomie einer Ophthalmia hepatica *Arch Augenheilk 31* 393–407
Klein E Dokert B Dressel H Renger F & Marre E (1972) Untersuchungen uber die Dunkeladaptation und den Farbensinn bei Patienten mit chronischen Leber erkrankungen *Dtsch GesundWes 27* 377–381
Klein S Dokert B Marre E Renger F & Westermann K (1974) Untersuchungen zur therapeutischen Beeinflussbarkeit der Hell Dunkel Adaptations und Farbsinn storungen bei chronischen Lebererkrankungen durch Vitamin A *Z ges inn Med 29* 485–487
Saraux H Labet R & Biais B (1966) Aspects actuels de la névrite optique de l ethylique *Ann Oculist (Paris) 199* 943–954
Smith J W & Brinton G A (1971) Color vision defects in alcoholism *Quart J Stud Alc 32* 41–44
Toews R R & Basu P K (1962) The jaundiced eye as a source of donor material *Brit J Ophthal 46* 523–527
Verriest G (1963) Further studies on acquired deficiency of colour discrimination *J opt Soc Amer 53* 185–195

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VERTICAL STEPS IN ISOPTERS AT THE HEMIOPIC BORDER – IN NORMAL AND GLAUCOMATOUS EYES

BY

LARS DAMGAARD-JENSEN

Careful perimetry disclosed small steps in peripheral isopters corresponding to the vertical meridian in about 50 % of normal eyes as well as eyes with glaucomatous field defects Most steps were found inferiorly The contraction of the isopter was always found on the nasal side of the field apart from a few of the glaucomatous eyes all of which also showed central field defects
The findings suggest that no significance with regard to pathology can be attached to small peripheral steps at the vertical meridian provided that the temporal hemifield is the greater Steps showing preponderance of the nasal half of the field however should arouse suspicion of an existing pathology
The reported observation as well as findings in the literature concerning function anatomy and pathology suggest that the nasal hemiretina is dominant over the temporal one

Key words perimetry – temporal field preponderance – isopters – normal – glaucoma – hemiopic border

Little attention has been paid to the anatomical functional pathological and evolutionary differences which exist between the nasal and the temporal hemi retina

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In 1913 Wessely (in a lecture never published but quoted by Kollner in 1914) noted that when one eye is tightly covered (e g by the palm) while the other eye is only closed so that light perception with it is still possible the light will be projected to the temporal side of the latter eye Kollner (1914) indicated that if a white screen is regarded after the eyes have been shut the binocular visual field on opening the eyes will to some individuals momentarily be divided into two by a vertical midline This is provided that differently coloured glasses are worn The right half of the binocular field assumes the colour of the right glass and vice versa

Brændstrup (1948) demonstrated functional hemiretinal differences by means of pressure phosphenes The differences in the phosphene field were less pronounced that those found by perimetry and campimetry By means of literature review and in the thought provoking discussion of his own work he further stressed the structural physiologic and pathologic hemiretinal differences Binder & Arendt (1965) stated that the phenomenon found by Kollner is constantly maintained in exotropes whereas in esotropes bitemporal sup

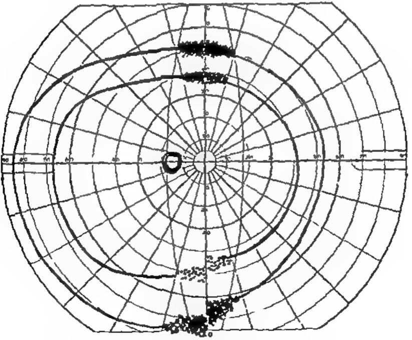


Fig 1
Visual field of a normal left eye Inferior vertical step

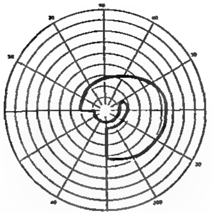


Fig 2

Visual field of a glaucomatous right eye (Rønne 1909) Vertical and nasal step
Temporal field preponderance

pression is found Ehlers (1976) indicated three methods of demonstrating the hemiopic border in normal eyes 1) by Wessely's method 2) by supplementing the above mentioned method of Kollner by fixating a close object e g a fingertip In this situation of convergence the division of the binocular visual field can be maintained And 3) by campimetry with two horisontally disparate objects A normal person will be able to see only one object peripherally along the vertical meridian whereas in other parts of the field he can distinguish two objects The present investigation shows that one further simple method is applicable by careful perimetry (see Material and Methods) about 50 % of normal fields will exhibit small steps at the vertical meridian (Fig 1)

Many authors have shown examples of vertical steps at the vertical meridian both peripherally and centrally but only rarely have these been the subject of discussion Rønne (1909) depicted 45 glaucomatous fields of which 10 % exhibited hemiopic border steps (Fig 2) In Traquair's Clinical Perimetry (1942) 36 % of the shown glaucomatous fields exhibited hemiopia line defects Lynn (1975) found vertical steps in 20 % of glaucoma fields with the defective area twice as frequent in the nasal as in the temporal field He was the first to stress the existence of glaucomatous hemiopic line disparities

This investigation was originally meant to focus on hemiopic defects in glaucoma However it was incidentally found that many normal eyes exhibit small vertical steps in peripheral isopters and consequently attention was also focused on the nature of these steps in normal eyes

Material and Methods

40 normal eyes (30 persons) and 45 glaucomatous eyes (27 persons) were examined by Goldmann kinetic perimetry A further 16 normal eyes (12 persons) were scrutinously examined by kinetic perimetry exclusively at the inferior part of vertical meridian

Kinetic perimetry was performed with white objects under standard conditions (maximal luminance 1000 Asb background luminance 31 5 Asb correction of refractional errors on examining isopters within 30° test object moving at a constant speed from non seeing to seeing parts perpendicular to the isopter) The vertical meridian itself was never used as a test track On examining normal eyes (as in Fig 1) thirty points were plotted in the 15° on either side of he vertical meridian Vertical steps were demonstrated by repeatedly moving the object at right angles to the vertical meridian in the suspected area (Fig 3) (This technique of searching meridional steps was first described by Ronne (1909) and published in his original investigations on glaucomatous nasal steps) The points were not connected in the usual way to make an isopter curve but were left unjoined thus enabling a visual estimation of the results to be made (Fig 1)

This technique was also applied along the other meridians but it was never possible to find similar steps elsewhere with the exception that the greatest step was sometimes found at the meridian situated 5 degrees to the temporal side of the lower vertical one

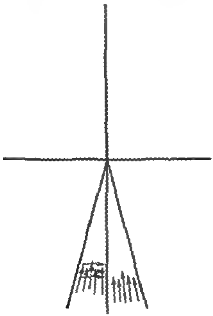


Fig 3
Technique of demonstrating meridional steps of peripheral field

Table I

Vertical steps in peripheral isopters of 40 normal eyes

Total	Inf	Sup	Inf + sup	Inverse steps
21 (52 5 %)	17 (42.5 %)	1 (2 5 %)	3 (7 5 %)	0 (0 0 %)

Inverse signifies nasal field preponderance see text for explanation

Results

Of the 40 normal eyes (Table I) 21 (52 5 %) exhibited small peripheral vertical steps similar to the one depicted in Fig 1 17 (42 5 %) only inferiorly 1 (2 5 %) only superiorly and 3 (7 5 %) both inferiorly and superiorly In all cases the temporal field was the larger one

Of the 45 glaucomatous eyes 16 showed no central field defects (Table II) 8 of those (50 %) exhibited vertical steps 5 (31 3 %) inferiorly 2 (12 5 %) superiorly and 1 (6 3 %) both superiorly and inferiorly No steps demonstrated nasal field preponderance which will be referred to as inverse steps

The remaining 29 glaucomatous eyes had central field defects ranging from enlargement of the blind spot to large defects breaking through to the peripheral isopters (Table III) 13 of the central defects extended to or beyond the vertical meridian 8 of those exhibited vertical steps (Fig 4)

17 (58 6 %) of the 29 eyes with central defects exhibited peripheral steps 8 (27 6 %) showed vertical steps inferiorly The same was the case superiorly with 5 eyes (17 2 %) and inferiorly + superiorly with 4 eyes (13 8 %) In 8 eyes (27 6 %) central steps were found 2 (11 8 % of all the peripheral steps) inverse peripheral steps and 4 (50 0 % of all the central steps) inverse" central steps were found

Table II

Vertical steps of 16 glaucomatous eyes without central defects

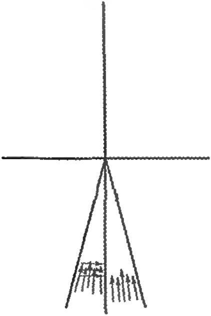
Total	Inf	Sup	Inf + sup	Inverse steps
8 (50 0 %)	5 (31.3 %)	2 (12 5 %)	1 (6 3 %)	0 (0 0 %)

Material and Methods

40 normal eyes (30 persons) and 45 glaucomatous eyes (27 persons) were examined by Goldmann kinetic perimetry. A further 16 normal eyes (12 persons) were scrutinously examined by kinetic perimetry exclusively at the inferior part of vertical meridian.

Kinetic perimetry was performed with white objects under standard conditions (maximal luminance 1000 Asb, background luminance 31.5 Asb, correction of refractional errors on examining isopters within 30°, test object moving at a constant speed from non-seeing to seeing parts perpendicular to the isopter). The vertical meridian itself was never used as a test track. On examining normal eyes (as in Fig. 1) thirty points were plotted in the 15° on either side of he vertical meridian. Vertical steps were demonstrated by repeatedly moving the object at right angles to the vertical meridian in the suspected area (Fig. 3). (This technique of searching meridional steps was first described by Rønne (1909) and published in his original investigations on glaucomatous nasal steps). The points were not connected in the usual way to make an isopter curve, but were left unjoined thus enabling a visual estimation of the results to be made (Fig. 1).

This technique was also applied along the other meridians but it was never possible to find similar steps elsewhere, with the exception that the greatest step was sometimes found at the meridian situated 5 degrees to the temporal side of the lower vertical one.



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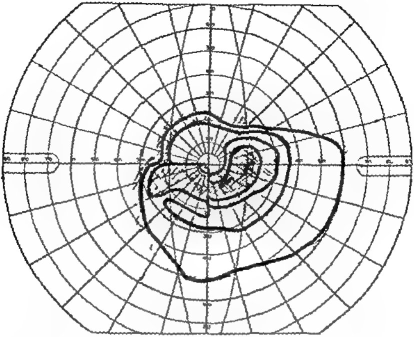

Fig. 4

Glaucomatous visual field of a right eye. Vertical steps of central defects

An attempt was made to statistically demonstrate significance of the vertical steps in normal eyes. 16 normal eyes were examined with object I/4. 16 times each of 10 meridians was plotted 25° to either side of the vertical meridian. The mean distance from the center was compared (Student's *t* test) with the mean of the neighbouring fields (Fig. 5). In 8 (50 %) of those eyes *there was a difference between the means of the isopter points closest to the*

Table III

Vertical steps of 29 glaucomatous eyes with central field defects

Total periph	Inf	Sup	Inf + sup	Central	Inverse periph	Inverse central
17 (58.6 %)	8 (27.6 %)	5 (17.2 %)	4 (13.8 %)	8 (27.6 %)	2 (11.8 %)	4 (50.0 %)

% of total (29) except concerning inverse steps. Here the 11.8 % and 50 % indicate the percentage of total peripheral (17) and central (8) steps respectively.

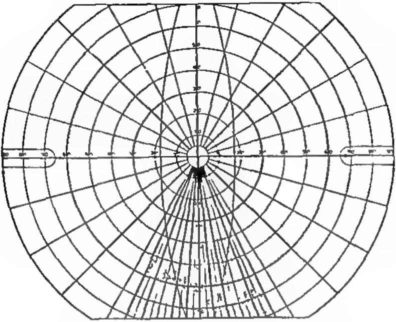

Fig 5
Vertical step of a normal right eye Repeated plottings in several meridians for statistical estimation (see Table IV)

vertical meridian 4 of the 8 eyes with steps showed greater dispersion i e greater standard deviation of the test point distances from the center of the field of the test marks close to the vertical meridian than elsewhere (cf the s values of Table IV) Table IV shows t and P values of consecutively per formed t tests along neighbouring meridians in a single person Table V shows the P values of all 8 eyes The results shown in Table V clearly demonstrate that the slope of the isopter curve is most pronounced at the vertical meridian or the meridian 5° temporal to that

Discussion

This study demonstrates that small vertical steps in peripheral isopters are frequently found provided that attention is focused on it The temporal field always is the larger in the examined normal eyes Most steps are found in feriorly No significant difference is found between the number of steps in normal and glaucomatous eyes Steps due to nasal field preponderance (in verse steps) are found only in the glaucoma eyes with central defects Fur

Table IV
Statistic evaluation of fig. 4

		nasal ← vertical ↓ meridian → temporal								
Meridian	247.5°	252.5°	257.5°	262.5°	267.5°	272.5°	277.5°	282.5°	287.5°	292.5°
m	55.40	60.13	56.56	57.41	58.61	63.19	65.61	66.66	67.05	69.[illegible]2
s	1.74	1.73	1.68	2.09	3.27	4.03	2.74	1.59	2.04	1.91
t		1.70	0.72	1.97	1.99	3.53	2.01	1.91	1.43	1.24
P		< 0.10	< 0.[illegible]	< 0.10	< 0.10	< 0.005	< 0.10	< 0.10	< 0.20	< 0.30

m = mean distance of test points from center
s = standard deviation
Student's t test has been applied (2 P level)

Table V

Significance levels for differences between neighbouring meridians for 8 normal eyes

		nasal ←			vertical ↓ meridian			→ temporal		
Eye no	247.5°	252.5°	257.5°	262.5°	267.5°	272.5°	277.5°	282.5°	287.5°	292.5°
1		< 0.70	< 0.95	< 0.95	< 0.98	< 0.02	< 0.30	< 0.10	< 0.[illegible]0	< 0.30
2		< 0.80	< 0.70	< 0.30	< 0.70	< 0.005	< 0.001	< 0.005	< 0.50	< 0.98
3		< 0.70	< 0.10	< 0.50	< 0.98	< 0.05	< 0.001	< 0.10	< 0.10	< 0.98
4		< 0.30	< 0.60	< 0.60	< 0.50	< 0.00	< 0.005	< 0.05	< 0.90	< 0.90
5		< 0.30	< 0.70	< 0.10	< 0.90	< 0.003	< 0.001	< 0.60	< 0.05	< 0.60
6		< 0.05	< 0.02	< 0.30	< 0.0	< 0.02	< 0.05	< 0.20	< 0.70	< 0.20
7		< 0.70	< 0.005	< 0.01	< 0.025	< 0.001	< 0.05	< 0.99	< 0.40	< 0.70
8		< 0.30	< 0.50	< 0.30	< 0.30	< 0.005	< 0.10	< 0.30	< 0.70	< 0.30

For explanation see text Fig , and Table IV

thermore the steps in the glaucoma eyes are often greater than those found in the normal eyes Consequently greater steps and steps with nasal field preponderance should arouse suspicion of a pathological process

Goldmann kinetic perimetry is reliable and the isopter curves are reproduceable Nevertheless numerous sources of error exist as regards examinator and examinee Undoubtedly various examinators with the above mentioned technique will find various numbers and sizes of vertical steps Review of the routinely obtained visual fields of this department disclosed in a few cases vertical steps in non glaucomatous eyes (found by the most scroutinous examinators)

It is not within the frames of this work to settle the question as to whether the explanation of the psysiological and pathological hemiretinal differences are to be found in the retina itself or in the visual pathway or in both Further investigations may solve this question and perhaps disclose further differences (e g static perimetry adaptometry ERG EOG VER or colour vision studies) And yet it is possible that the hemiretinal differences can only be revealed by the kinetic technique

An object moving from one side of the visual field to the other changes on reaching the vertical meridian from being projected to one brain half to being projected to the other one This change takes place unnoticed Visual stimuli of neighbouring retinal receptive fields at the vertical meridian of the cat are relayed alternately to area 17 of one occipital pole and area 18 of the other one (Leicester 1968) Possibly a similar phenomenon is found in humans cf the greater dispersion of the test marks close to the vertical meridian seen in Fig 5 Berlucchi & Rizzolatti (1968) showed that in split chiasm cats the receptive area of visual cortex cells at the border between area 17 and area 18 receives both uncrossed (geniculocalcarine) and crossed (callosal) fibres The reason why this change of projection does not arouse confusion according to Ehlers (1971 1974) possibly is that inhibitory occipito occipital fibres pass between the two hemispheres through the corpus callosum

Cogan (1974) in patients with moderate arterial hypertension found that arteriolar calibre changes were confined to the nasal hemiretina a fact suggesting a difference in vascularisation between the two hemiretinae Different vascularisation of the two hemiretinae does not explain hemiopic steps in normal eyes but is a possible factor in the development of glaucoma defects Best et al (1972) found numerous choriodal filling defects by fluorescein angiography in glaucomatous eyes with intraocular pressure artificially raised to 60 mmHg They found a direct relationship between the filling defects and visual field defects the former were all present in the temporal hemiretina and the latter were consequently all found in the nasal hemifield

Østerberg (1935) found a higher density of photoreceptors nasally than temporally. This may be part of the explanation of the nasal hemiretinal preponderance in normal individuals. The greater clinical resistance of the nasal hemiretina (cf. the temporal island of ultimate glaucoma stages) in glaucoma might partly be due to the same fact. Some of the central and greater peripheral vertical steps of glaucoma eyes may assume the following course. The field defects approach the vertical meridian from the relatively frail nasal hemifield, reach it, and for some time remain there because of a greater resistance of the temporal hemifield. The temporal part of the visual pathway (uncrossed fibres) phylogenetically is the younger one. Brown Sequard (quoted by Haglund 1952) was the first to describe the great vulnerability of higher but phylogenetically younger brain tissue as compared with that of the phylogenetically older tissue. Perhaps some differences in vulnerability between the crossed and uncrossed parts of the visual pathways manifest themselves in glaucoma. Although the crossed and the uncrossed part of the visual pathway microscopically seem much alike, there is a tremendous difference in their phylogenetic age.

References

Berlucchi G & Rizzolatti G (1968) Binocularly driven neurons in visual cortex of split chiasm cats. *Science 159*, 308–310.

Best M, Blumenthal M, Galin M A & Toyofuku H (1972) Fluorescein angiography during induced ocular hypertension in glaucoma. *Brit J Ophthal 56*, 6–12.

Binder H F & Arndt C L (1963) Binocularity in anomalous retinal correspondence. *Acta ophthal (Kbh) 41*, 653–658.

Brændstrup P (1949) The functional and anatomical differences between the nasal and temporal parts of the retina. *Acta ophthal (Kbh) 26*, 351–361.

Cogan D G (1974) *Ophthalmic manifestations of systemic vascular disease*. Saunders, Philadelphia, pp 74–78.

Ehlers N (1971) An extramacular inhibition phenomenon demonstrating the hemiopic border in normal subjects. *Acta neurol scand Suppl 43*, 265–266.

Ehlers N (1973) Importance of callosal transfer in the extramacular inhibition phenomenon along the hemiopic border. *Acta ophthal (Kbh) Suppl 120*, 82–86.

Ehlers N (1974) Two object inhibition along the hemianopic border. *L'annee therapeutique et clinique en ophthalmologie*. Libraire Fueri lamy, Marseilles 25, pp 471–477.

Ehlers N (1976) Demonstration of the hemiopic border in normal persons. *Acta ophthal (Kbh) 54*, 198–202.

Haglund G (1952) Massive brain damage after acute anoxia. *Acta chir scand 102*, 364–373.

Kollner H (1914) Das funktionelle Überwiegen der nasalen Netzhauthalfte im gemein schaftlichen Sefeld *Arch f Augenheilk 76* 153–164
Leicester J (1968) Projection of visual vertical meridian to cerebral cortex of the cat. *J Neurophysiol 31* 371–382
Lynn J R (1975) *Testing the visual field in glaucoma* Symposium on glaucoma Mosby Saint Louis pp 111–150
Ronne H (1909) Defects of nasal field in glaucoma *A v Graefes Arch Ophthal 71* 52–69
Ronne H (1909) Über das Gesichtsfeld beim Glaukom *Klin Mbl Augenheilk 47* 12–33
Traquair H M (1942) *An introduction to clinical perimetry* Henry Kimpton London 114–139
Østerberg G (1935) Topography of the layer of rods and cones in the human retina *Acta ophthal (Kbh) Suppl 6* pp 102

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SOME ESSENTIAL OPTICAL FEATURES OF THE ZEISS FUNDUS CAMERA

BY

BO BENGTSSON and C E T KRAKAU

The imaging system of the Zeiss fundus camera comprises a front lens and a mirror with a central opening in the anterior focus of a camera objective Focusing is achieved by changing the distance between the film and the camera objective The principal point of the examined eye is imaged in the central opening of the mirror when the camera is correctly positioned By applying reasoning current in elementary geometrical optics it was found
1) that both the absolute and the relative magnification depend on the reduzierte Axenlangenkonvergenz only
2) that it is possible to correct the influence of refraction on magnification and
3) that the relation between the camera extension needed to provide sharp pictures and the principal point refraction of the examined eye is linear The validity and practical importance of those findings as well as transcleral illumination and theoretical resolving power are briefly discussed

Key words Fundus camera – fundus photography – magnification – refraction – focusing – resolving power – illumination

The camera intended for photographing the fundus of the eye described by Nordenson and manufactured by Zeiss Jena was designed on the same principles as Gullstrand s reflex free ophthalmoscope An instrument highly

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improved regarding essential points was developed after the second World War by Zeiss Oberkochen This excellent instrument has dominated the market since it was introduced by Littman in 1955 and is now to be found in most large eye clinics in the world Getting good fundus pictures is within easy reach of everyone without much training and fundus photography is nowadays a routine method in the eye doctor s practice

Littman s paper and the manufacturer s instruction manual describe the principle of the camera and give good guidance as to its use Suggestions for achieving consistently good pictures (Allen 1964) and reliable image size measurements (Behrendt & Doyle 1965) have later been added

In connection with a general ophthalmic population survey photography of the eye ground was routinely performed in a great number of persons (Bengtsson 1976) In dealing with this material it was felt that a somewhat more precise knowledge of the properties of the camera was needed than is provided in the publications quoted By applying reasoning current in optics it is possible to reach an understanding of some of the essential features of the Zeiss fundus camera Though important from a practical point of view these facts are not generally known to ophthalmologists so there seems to be some justification for the present description

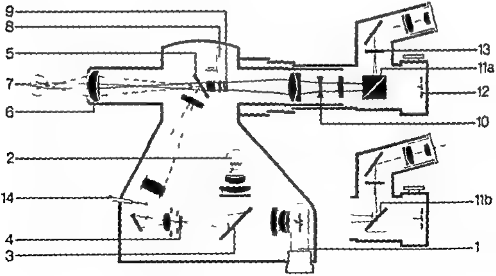

Fig 1
Manufacturer s diagram of the fundus camera (see text)

Principle

The optical solution to the problem of photographing the eye ground is similar to indirect ophthalmoscopy in that in both cases a positive lens – the front lens (Fig 1 6) is used This lens has the double function of producing a) a cone of light suited for the illumination of the fundus and b) an aerial image of the eye ground between the front lens and the camera objective (Fig 1 10) or the observer respectively

The *illuminating system* in the modern Zeiss camera consists of a filament bulb (Fig 1 2) for adjustment and a flash tube (Fig 1 1) for film exposure Both are focused on three levels in succession first on a glass plate (1 4) then on a mirror (1 5) with a central hole and finally on the patient s eye (1 7) The large diameter of the front lens and the short distance to the patient s eye allow illumination of more than 30 degrees of the retinal surface

The *imaging system* comprises the patient s eye the front lens the mirror with a central hole the camera objective and the film (Fig 1 12) The front lens forms an aerial image which is projected on to the film by the camera objective The distance between the latter and the film plane is changed by telescoping the camera housing until a sharp image is obtained in the operator s eye piece which corresponds to a sharp image on the film plane

The anterior focal level of the camera objective falls in the central hole of the mirror The effect of this socalled *telecentric system* is clear from Fig 3 The central beam of the bundle from an image point will be parallel to the camera axis after passing through the hole and the camera objective If the film plane is out of focus the magnification will remain uninfluenced The image will then be blurred

The Distance from the Camera to the Examined Eye

As indicated in the instruction manual a ring of light surrounding a non illuminated *center enters the eye*

The non illuminated center is produced by a disclike central mask, imprinted on the glassplate (Fig 1 4) located at the level of the first aerial image of the light source The mask is reproduced on the mirror (Fig 1 5) – where it considerably overlaps the central opening A second image of the mask arises in front of the camera along with the third image of the light source which should be positioned on the corneal surface

Apertures on a wheel situated about one cm past the glass plate (Fig 1 4) move the waist of the light bundle emerging from the camera a few milli

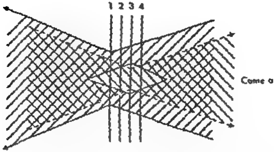

Fig 2

Bundles of outgoing (////) and incoming (\\\\) light in front of the camera
1 Waist 2 Blue haze 3 Optimal separation 4 Red haze

meters forwards past the sharp image of the mask – into the pupil level of the subject's eye

In order to reach the film light emerging from the observed fundus has to pass through the central opening in the mirror (Fig 1 5) At the level of the corneal surface this is possible only for light passing parts of the non illuminated center corresponding to a hypothetical image of the opening and distinctly separated from the illuminated periphery when the camera is in the right position This area about 2 mm in diameter is the entrance pupil of the camera (Fig 2)

As a result of this ingenious construction disturbances from light dispersed at the transition from air to the tear film on entering the examined eye can be avoided If the camera gets too far away from (or close to) the subject's eye however a blue (or red) haze of light spreads across the picture The explanation is of course that light dispersed at the corneal surface from the inner border of the light ring mixes with light emerging from the fundus enters the camera and reaches the film (Fig 2) Anyone who inserts and observes a white paper in front of the camera can make sure that the inner border of the light ring is of the right colour

The light ring enters the eye peripheral to and therefore somewhat behind the vertex cornea The free region between the blue and red hazes is very narrow – 3 mm at best Therefore we consider the central opening in the mirror to be imaged in the principal plane of the subject's eye (The two principal planes of the eye are so near each other that they are taken together)

In order to allow the adjustment and flash light to enter the eye the pupil has to be dilated In cases of glaucoma with miotic therapy there are often difficulties in getting the pupil sufficiently wide for photography of the pupil lary region However since the pupil in these cases is often wide enough not

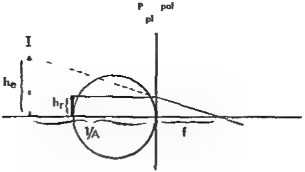

Fig 4
Formation of an image of a retinal structure

For the *front lens* we have $M_f = \frac{h_f}{h_e} = \frac{f_f}{1/A + d} = \frac{x}{f_f}$ (2)

where d is the distance between the principal plane of the eye and the anterior focal plane of a frontal lens with the focal length f_f which creates an image (II) with the height h_f (Fig 5)

For the *camera objective* we have $M_c = \frac{h}{h_f} = \frac{f_c}{y} = \frac{z}{f_c}$ (3)

where y = the distance from the image (II) to the anterior focal plane of a camera objective with a focal length f_c. The final image (III) with the height h_c is created on the film at a distance z from the posterior focal plane (Fig 5)

Since the first focal point of the camera lens falls at a distance $x + y$ *from* the focal point of the front lens we get

$$f_f = d\,(x + y) \tag{4}$$

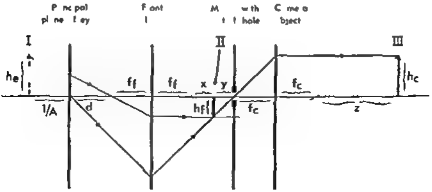

Fig 5
The imaging system of the fundus camera

Elimination of x from eqs 2 and 4 gives

$$y = \frac{f_f}{d}\left(\frac{1}{1 + Ad}\right) \tag{5}$$

Eliminating y from eqs 3 and 5 we get

$$z = \frac{f_e}{f_f} d\,(1 + Ad) \tag{6}$$

The total magnification is then (eqs 1 2 3 and 6)

$$M = M_e \quad M_f \quad M = \frac{1/A + f}{f} \quad \frac{f_f}{1/A + d} \quad \frac{f_e d\,(1 + Ad)}{f_f} = \frac{f\,d}{f_f}\left(A + \frac{1}{f}\right) \tag{7}$$

In this formula f_f and f_e are always constants d is a constant if the camera is correctly positioned in relation to the patient The *total magnification* is then

$$M = k\,(A + 1/f) \quad \text{where k is a constant} \tag{7 a}$$

Let m denote the magnification in an emmetropic eye ($A = 0$) which has the normal refractive power $1/\bar{f}$ The *relative magnification* is then

$$M_{rel} = \frac{M}{m} = (A + 1/f)\,\bar{f} \tag{8}$$

In case we are dealing with purely *axial emmetropia* we have $f = \bar{f}$ and eq 8 takes the form

$$M_{rel} = 1 + A\bar{f} \tag{8 a}$$

The value of $\bar{f}$ given by Gullstrand for his exact schematic eye is 0 01705 m Using this value in eq (8 a) we obtained excellent agreement with a list of magnifications in nine points four diopters apart courteously specified by the manufacturer (Table I)

Table I

The influence of refraction on magnification Comparison between calculated values and manufacturer s specifications

Zeiss values			$1 + A\bar{f}$
A	M	M_{rel}	
+16	3 10	1 28	1 27
+12	2 93	1 21	1 20
+ 8	2 76	1 14	1 14
+ 4	2 60	1 07	1 07
0	2 43	1 00	1 00
− 4	2 27	0 93	0 93
− 8	2 11	0 87	0 86
−12	1 95	0 80	0 80
−16	1 79	0 74	0 73

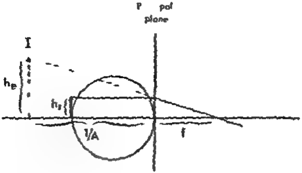

Fig 4
Formation of an image of a retinal structure

For the *front lens* we have $M_f = \dfrac{h_f}{h_e} = \dfrac{f_f}{1/A + d} = \dfrac{x}{f_f}$ (2)

where d is the distance between the principal plane of the eye and the anterior focal plane of a frontal lens with the focal length f_f which creates an image (II) with the height h_f (Fig 5)

For the *camera objective* we have $M_o = \dfrac{h_c}{h_f} = \dfrac{f_c}{y} = \dfrac{z}{f_c}$ (3)

where y is the distance from the image (II) to the anterior focal plane of a camera objective with a focal length f_c The final image (III) with the height h is created on the film at a distance z from the posterior focal plane (Fig 5)

Since the first focal point of the camera lens falls at a distance x + y from the focal point of the front lens we get

$$f_f = d(x + y) \quad (4)$$

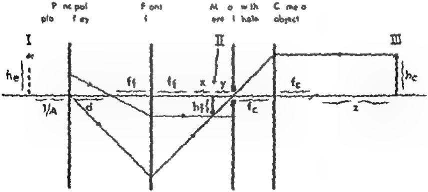

Fig 5
The imaging system of the fundus camera

$$z_0 - z_A = \left(\frac{f_c d}{f_f}\right) A$$

when an ametropic eye of refraction A is photographed

If A is put zero in eq (7) the total magnification m under emmetropic and normal refractive power conditions is found to be

$$m = \frac{f\ d}{f_f \bar{f}}$$

According to the manufacturer m is 2 48 Since $\bar{f} = 0\ 01/0\ 55$ the change of extension is

$$\frac{z_0 - z_A}{A} = (m\ \bar{f}) = 1\ 72 \text{ mm/dpt}$$

The total extension of the camera is 58 mm an adjustment which covers the range –16 to +17 dpt. i e a range of about 33 dpt This means 1 76 mm/dpt which is in reasonable agreement with the calculated value

Many photographers with a very flexible accommodative power have a very difficult time getting any of their pictures in sharp focus (Allen 1964) However knowing the refraction of the eye under investigation we can preadjust the camera to a position which provides sharp images We have explored this possibility by mounting a simple scale to the extension tube This turned out to simplify the routine work and improve the quality of the photographs considerably

References

Allen L. (1964) Ocular fundus photography Suggestions for achieving consistently good pictures and instructions for stereoscopic photography *Amer J Ophthal 57* 13–28

Behrendt T & Doyle K E. (1965) Reliability of image size measurements in the new Zeiss fundus camera *Amer J Ophthal 59* 896–899

Bengtsson B (1976) The variation and covariation of cup and disc diameters *Acta ophthal (Kbh) 54* 804–818

Gullstrand A. (1891) Om samtidig bestamning af refraktion och synskarpa *Nord Med Arkiv Band XXIII Nr 9* 1–46

Littmann H (1955) Die Zeiss Funduskamera *Bericht d Ophthalm Ges LIX* 318–321

Stenstrom S (1946) Untersuchungen uber die Variation und Kovariation der optischen Elemente des menschlichen Auges *Acta ophthal (Kbh) Suppl XXVI*

Stromberg E. (1936) Über Refraktion und Achsenlange des menschlichen Auges *Acta ophthal (Kbh) 14* 281–293

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Gullstrand introduced the concept "reduzierte Axenlangenkonvergenz" defined as $B = A + D$ where D is the refractive power of the eye ($= \frac{1}{\bar{f}}$). In this *notation the total and relative magnification can be written* $M = kB$ and $M_{rel} = B\bar{f}$ respectively.

Thus both the absolute and relative magnification depend on the "reduzierte Axenlangenkonvergenz" B only. By definition B remains constant in a pure *refraction ametropia* and according to Gullstrand (1891) accommodation does not influence B. *In corneal astigmatism* B is the same in the two main meridians (Gullstrand 1891). Provided the astigmatism correcting device of the camera is not utilized the magnification is consequently the same in the two main meridians though there is some blurring in one or both meridians. *Thus for example a circular optic disc in an astigmatic eye remains* circular on the photograph. On the other hand if optimal sharpness is obtained by use of the astigmatism correcting device f_e is changed and a deformation is introduced.

The problem of finding the size of fundus structures in absolute measure is *obviously equivalent to estimating the "reduzierte Axenlangenkonvergenz" B* i.e. the sum of A and D. A is easily determined whereas D is generally out of reach. A is strongly correlated to B ($r_{AB} = 0.8$), D less so ($r_{DB} = 0.6$) but as has been shown by Stromberg (1936) and Stenstrom (1946) A and D are uncorrelated.

If we estimate B by inserting the value for A and accept a "*normal*" value ($1/\bar{f}$) for D we can expect to get rid of about $^2/_3$ of those variations in magnification which are caused by variations in the optical properties of the examined eye.

Calculation of the glass refraction G from the principal point refraction A and vice versa can be *done* by means of the formulas

$$G = \frac{A}{1 + A\bar{f}} \text{ and } A = \frac{G}{1 - G\bar{f}}$$

which gives directly $1 + A\bar{f} = 1/(1 - \bar{f}G)$. By multiplication of the result of length measurements on eye ground photographs by the factor *(1–0.01 035G)* it is possible to correct the influence of refraction on magnification which was done by Bengtsson (1976).

Camera Extension

Eq. *6 shows that the relation between extension and principal point refraction* is linear. This means that if the camera is adjusted for an emmetropic eye the camera extension has to be changed by a distance

Key words bloody tears – haemolacria – lacrimae cruentae – conjunctival cytology – erythrocytes – chemical detection of blood in tears – occult bleeding

Psychic tears are provoked by deep sorrow or emotion Blood indicates mutila tion perhaps death The fear seizing laymen at the sight of bloody tears is *not surprising*

In one of Dostojevski s works bloody tears are mentioned Foma Fomitsj the villain and parasite usurps command of his uncle s estate This gives occasion for the following indignant exclamation This will cost your uncle bloody tears – indeed – bloody tears he will cry the colonel

I have seen no more than a single case of manifest bloody tears The patient was an 8 year old girl whose parents greatly alarmed telephoned and reported the phenomenon On arrival at the clinic bloody tears continued to roll down the child s cheek The phenomenon disappeared following local antibiotic treat ment of the concurrent bacterial conjunctivitis

Few cases of bloody tears have been reported in the professional literature Such tears may have many different causes Acute hyperaemia and inflamed conjunctiva tumours (angioma teleangiectasia) manipulation or chemical treat ment of the conjunctiva (follicle expression in trachoma Crede s prophylaxis with $AgNO_3$ mecholyl test) crab lice along the ciliary margin vicarious menstruation and epistaxis with a retrograde blood stream into the conjunctiva through the puncta lacrimalia (Banta & Seltzer 1973)

The object of the present study was to determine suitable methods for dis closing relatively small quantities of blood in tears This can be performed by microscopy which demonstrates erythrocytes in aspirated tear secretion The sampling procedure should be sufficiently delicate so as not to cause artificial bleeding

A stix method (Gasset 1960) can reveal glucose and ketones in tears Similarly a stix method has been developed for the chemical detection of haemolacria (Norn 1974)

Microscopically Detected Haemolacria

Erythrocytes are often seen in conjunctival smears Deep scraping with a plati num spatula or knife may however cause artificial bleeding This method is therefore unsuitable for disclosing occult haemolacria

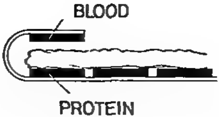

Fig 1

Chemical analysis of blood and protein in tears by means of the Hema combistix (Ames) The conjunctival fluid is transferred to a cotton plug which is then placed between the test field for blood and that for protein

The blood stain is generally seen as spots of different sizes surrounded by a yellowish white field The maximally coloured spot is the one estimated

The protein field is then read (reading time not critical) The scale on the packing ranges from yellowish green to bluish green over five steps corresponding to 0 1–0 3–1 0–3 0–10 mg protein per millilitre

Comments In a similar stix test for glucose Gasset (1969) used Schirmer's test paper for suction of conjunctival fluid In preliminary tests much less blood and protein was noticed when using Schirmer's paper as compared with cotton The harmless and effectively sucking cotton plug is therefore to be preferred for blood tests

Sources of error Maximum greenish blue stain from the protein test field might possibly penetrate through the cotton and give an artificial colouring to the blood area However such penetration has never been observed, the stain passes only superficially into the cotton

The two test fields are placed at the same level and opposite to each other round the cotton plug to render the fluid yields identical

Very fine blue dots may be seen at the profound edge of the test area. These are due to the fixation of the area to the transparent stix Such dots are not included in the reading

Chemistry The blood test area has been impregnated with peroxide and o toluidine The positive colour reaction is due to the peroxidase of haemoglobin

The protein test field has been impregnated with tetrabromophenol blue (The hema combistix also has test areas for glucose and pH)

Material

An analysis for chemically detectable blood was carried out on 303 eyes from own practice One eye from each of 76 medical students was included in the normal material The diagnoses are shown in Table II

Table II

Chemically detectable haemolacria in diagnostic groups (Student's *t* test)
A total of 270 eyes. The remainder constitute smaller groups

	Chemical haemolacria (per cent)	t	*P*	n
Normal	3	–	–	115
Acute infect. conj.	21	3.73	< 0.001	69
Subchron. infect. conj.	20	2.33	< 0.05	15
Panophthalmia	75	5.36	< 0.02	4
Ciliary congestion	13	1.40	n.s.	15
Postoperatively 1st day	95	11.25	≪ 0.001	39
2nd day	30	6.0	< 0.01	5
6th day	13	1.4	n.s.	15

Clinical results

No more than 3 per cent out of 115 normal eyes showed chemically detectable haemolacria (Table II). This corresponds to the finding on microscopy of 100 erythrocytes or more in the normal material (3 per cent), while microscopy revealed one or more erythrocytes in as many as 13 per cent.

Chemical analysis, like microscopy, mainly disclosed blood in diseases due to bacteria (infectious conjunctivitis, panophthalmia).

In acute infectious conjunctivitis blood was more often detected by microscopy (65 per cent) than by chemical analysis (21 per cent). On the other hand in the subacute to chronic forms the percentage figures were approximately equal (26 and 20 respectively).

In cases of ciliary congestion (acute glaucoma, acute iritis) only a doubtful non significant rise in the blood content was noticed.

A number of patients were examined after operation for cataract, retinal detachment and for glaucoma. At the first change of dressing, the day after the operation, considerable quantities of blood were seen in all but two cases (both discission of after cataract).

Analysis on the second day showed moderate to small amounts of blood, and on the sixth day blood was present in a few cases only.

A small number of eyes affected by keratitis, meibomitis, blepharitis, dermato-conjunctivitis, simple conjunctivitis, etc. were examined. Chemically detectable blood was a comparatively rare occurrence in these cases.

The largest amounts of blood were found postoperatively In the clinical groups more than a weak positive reaction was rarely found

Experimental studies

Repeated examinations of 14 eyes without haemolacria provoked no chemically detectable bleeding

Intense rubbing of the eyes for 60 seconds gave a weak to moderate blood reaction in two out of 12 cases

Instillation of silver nitrate (0 5 % $AgNO_3$) provoked a weak blood reaction

Instilled ear vein blood would in normal individuals disappear in the course of 20–40 min

Protein and haemolacria

Protein was detected chemically in the conjunctival fluid from all eyes This proved that the fluid really had been sucked up by the cotton

The average amount found was 2 92 mg/ml (Stegman (1975) using refractometer found 3–7 mg/ml) The distribution is seen in Fig 2

The protein concentration was found to be raised in patients with haemolacria (3 62 mg/ml) but independent of the intensity of the blood reaction (strong reaction 3 43 mg/ml moderate 4 26 mg/ml and weak 3 18 mg/ml)

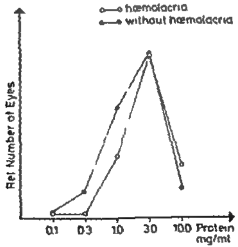

Fig 2

The protein concentration in tears from subjects with and without chemically detectable haemolacria

A protein concentration of not less than 3 mg/ml was found in 78 per cent with haemolacria as against 58 per cent without blood The difference is significant ($t = 2.76$ $P < 0.01$)

Discussion

Two different methods have been described above both of which were suitable for disclosing the presence of blood in the conjunctival fluid

The chemical stix method is the quicker and technically simpler method of the two whereas the microscopical analysis is the more sensitive The chemical method requires a minimum of 100 erythrocytes per 3 1 mm of conjunctival surface to give a positive reaction as estimated from the normal material

However the two methods are not directly comparable Microscopy reveals intact erythrocytes while the chemical method discloses the presence of haemoglobin and its breakdown *products derived from decomposed erythrocytes* This harmonize with the fact that the chemical method is relatively more often positive in subacute to chronic infectious conjunctivitis than in acute infectious conjunctivitis

Postoperatively occult blood may be seen for several days whereas experimentally instilled blood disappears in less than one hour This difference may be due to repeated postoperative haemorrhages but is more likely to be due to deficient drainage from the conjunctiva (dressing usually prescribed the first four postoperative days) and the considerable postoperative neutrophilia (owing to the surgical injury of tissue and the presence of sutures)

The *protein* concentration is raised in relation to the chemically detected haemolacria This is unlikely to be due to a positive protein reaction from haemoglobin because the protein concentration is independent of the blood concentration in haemolacria The increased amount of protein can more likely be accounted *for by exudation from the blood stream*

The results of microscopical and chemical analyses of tears for blood show that occult haemolacria is a *frequent* phenomenon It may even be seen in a small number of normal eyes with no detectable cause

The phenomenon is most frequently found with the group of *infectious conjunctivitis* with pus secretion and escape of neutrophilic granulocytes into the conjunctival sac Pronounced hyperaemia is an unlikely cause of blood in tears as this does not seem to occur in relation to marked ciliary congestion

The following mechanism is considered to be the most likely one Excessive

emigration of neutrophilic granulocytes (and to a lesser extent of lymphocytes) and exudation will open the conjunctival vessels to such a degree that erythro cytes will likewise escape into the conjunctival sac

The phenomenon of occult blood in tears could be used as a diagnostic tool Chemically detectable haemolacria suggests bacterial conjunctivitis The method is easy to perform but unfortunately not particularly sensitive

Microscopical analysis of erythrocytes is a more laborious method However the quantitatively studied sample gives additional information as to the occur rence of other cells of considerable diagnostic interest (neutrophilia lympho cytosis keratinized epithelial cells desquamation of columnar epithelial cells eosinophilic leucocytes etc (cf Norn 1960))

The clinical stix method could be used as a screening method in general diseases (haemophilia leucaemias etc)

References

Banta R G & Seltzer J L (1973) Bloody tears from epistaxis through the naso lacrimal ductus *Amer J Ophthal* 75 726–727

Dostojevski F M (1859) *Menneskene på Godset Stepantjikovo*

Gasset A R Braverman L E Flemming M C Arky R A & Alter B R (1968) Tear glucose detection of hyperglycemia *Amer J Ophthal* 65 414–420

Norn M S (1960) Cytology of the conjunctival fluid *Acta ophthal (Kbh) Suppl* 9 84–86

Norn M S (1974) *External Eye (Methods of Examination)* Scriptor Copenhagen p 119–120

Stegman R & Miller D (1975) A human model of allergic conjunctivitis *Arch Ophthal (Chicago)* 93 1354–1358

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PILOCARPINE-INDUCED SUBSENSITIVITY TO CARBACHOL AND PILOCARPINE OF CILIARY MUSCLE IN VERVET AND CYNOMOLGUS MONKEYS

BY

ERNST H. BÁRÁNY

Vervet monkeys were given unilateral treatment for two weeks with one 2% pilocarpine eye drop three times daily between 8 a.m. and 6 p.m. (night interval 14 h) and were then subjected to anterior chamber perfusion. 90 µg pilocarpine intracamerally caused similar and substantial increases in outflow facility in both eyes. Cynomolgus monkeys were unilaterally treated with continuous release of 33 µg/h of pilocarpine for 3–6 days. The facility response to 1 mg/kg pilocarpine i.v. was small or absent on the treated side.
Iridectomized cynomolgus monkeys responded with 1.6 ± 5.2 (SD) diopters accommodation to 1.5 mg/kg pilocarpine i.m. with very similar responses in the two eyes. During continuous release of 30 µg/h pilocarpine accommodation of the treated eye dropped gradually and after 4–8 days treatment the accommodative response was markedly reduced to pilocarpine 1.5 mg/kg i.m. or 100 µg topically. The degree of subsensitivity was much less when tested with either systemic or topical carbachol. This was also the case in a few vervet experiments. Recovery of full pilocarpine sensitivity took several weeks in the cynomolgus monkey.
As an explanation for the excessive subsensitivity and large interindividual differences found with pilocarpine an individually variable non-muscarinic relaxant action counteracting the muscarinic excitatory action is suggested. Clinical implications of this hypothesis are discussed.

Key words: pilocarpine – carbachol – outflow facility – accommodation – subsensitivity – ciliary muscle

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Auricchio & Diotallevi (1959) and Bito and his collaborators (1967–1971) have drawn attention to the cholinergic subsensitivity of the iris sphincter following only a few days of exposure to increased levels of the neurotransmitter acetyl choline Both cholinesterase inhibition with DFP and continuous light had the effect

Subsensitivity to cholinergics in the ciliary muscle evidently could be im portant in glaucoma treatment Kaufman & Barany therefore looked for and found subsensitivity of the accommodation response (1975) and the facility response to pilocarpine (1977) in the two monkey species Cercopithecus ethiops (vervet) and Macaca fascicularis (cynomolgus) after prolonged treatment (months) with ectothiophate This subsensitivity disappeared only very slowly *During the treatment period the eyes accommodated strongly which similarly* to the largely undisturbed light reflex in Bito s experiments must be due to a measure of balance between subsensitivity and potentiation of endogenous acetylcholine

Since both DFP and echothiophate are long acting cholinesterase inhibitors and since in sleep not only are the pupils constricted but accommodative tone also persists (Berggren & Wålinder 1969) then the cholinergic receptors in both Bito s iris sphincter and our ciliary muscle experiments were exposed to excess acethylcholine around the clock Experiments to test whether con tinuous exposure to pilocarpine also causes subsensitivity were difficult to organize until the advent of continuous release material developed by the ALZA Company The present paper describes subsensitivity following con tinuous pilocarpine administration for a few days to monkey eyes and virtual absence of subsensitivity in monkey eyes treated for two weeks with pilo carpine eye drops in the conventional manner These latter experiments were performed in 1966 but have never been reported

Methods

Animals For the facility studies in 1966 fully adult – old vervet monkeys Cercopithecus ethiops of both sexes were used Their eyes were previously untouched For the present facility and accommodation studies mainly cyno molgus monkeys (Macaca fascicularis) of both sexes around 2–3 kg body weight were used These animals were quite young A few vervets were also used The monkeys were kept in cages with a wire mesh front through which they could look at other monkeys across the room This tends to prevent cage myopia For the accommodation studies most of them had both eyes totally iridectomized as described by Kaufman & Lutjen Drecoll (1975)

Refraction was measured in a few initial experiments with the Thorner refractometer used by Tornqvist (1967) but the majority of measurements were made using a Zeiss Hartinger coincidence refractometer Both instruments were modified in the following way A small gear train was built to couple the shaft of a precision helical potentiometer (Helipot©) to the shaft of the instrument dial The potentiometer was fed with DC from a highly stabilized source Thus the voltage output was a constant function of the dial position and was recorded on a strip chart recorder During a drug experiment the observer alternately turned the refractometer to the right and left eye of the monkey and adjusted the dial several times but never actually read the refractions These were instead measured from the strip chart at the end of the experiment As a rule observations continued until the response started to decrease

In the few cases where more than minimal astigmatism was present the refractions for the two axes were averaged

The head of the animal was fixed in a holder and the body kept warm by means of a heating pad The lids were kept open with speculae and the corneae covered with plastic contact lenses −7 D This greatly facilitated the experiment since the corneae did not dry out and the minus range of the instrument was extended

Anaesthesia The mixture CI 744 an excellent anaesthetic in other respects was not ideal in the present case since the monkeys show bursts of accommodation under it (as under phencyclidine) The bursts could be suppressed by the addition of 10 mg/kg pentobarbital im to the usual dose 10 mg/kg CI 744 im This combination yields anaesthesia sufficient for refraction work for about 1½ h No cycloplegic refractions were done but it is likely that some ciliary muscle tone remains even with this anaesthesia

Facility measurements were done under pentobarbital anaesthesia with the standard technique of our laboratory (Barany 1966)

Topical drug treatment The commercial pilocarpine ocular therapeutic systems for human use (Ocusert® Pilo 20 or 40) are too large for the eyes of monkeys in our weight range An experimental constant release rate material releasing pilocarpine nitrate was made available which can be cut to any shape Like the Ocusert® systems these systems have a higher release rate on the first day but this can be avoided by leaching Following a suggestion by Dr Rudolph Hahnenberger pieces of this material were fastened to carriers placed in the conjunctival sac

The arrangement is shown in Fig 1 A 48 mm length of tubing (Dow Corning Silastic® 602 171 outer diameter 1 65 mm) carrying a 0 5 cm roughly

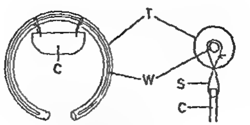


Fig 1
Device carrying continuous release material for insertion into monkey conjunctival sac T = tubing (Silastic®) S = silk sutures knot pulled into tubing W = stainless steel wire C = continuous release material

rectangular piece of pilocarpine releasing material and reinforced with a 40 mm piece of soft stainless steel wire diameter 0 4 mm was bent to fit into the conjunctival sac with the releasing material in the upper nasal fornix Some times a slight reduction in length was necessary The insert is well retained but it unfortunately happens that a corneal abrasion and corneal oedema is seen after a few days The devices were not sterilized before use A mild con junctival irritation was frequently seen with occasionally a more severe reaction

In the experiments of 1966 with a conventional eye drop regimen an ordi nary eye dropper was used and 1 drop of 2 % pilocarpine HCl placed onto the one cornea three times daily The monkey was not anaesthetized but re strained manually

Topical sensitivity testing in accommodation experiments The animal was re moved from its head holder and put with the eyes looking upwards The contact lenses were removed and the drug to be tested – dissolved to a volume of 5 μl – applied to the center of the cornea by means of a micrometric syringe The droplet was allowed to dry and the contact lenses replaced This procedure will be called drug put under the contact lenses

Drugs Doses refer to base Ordinary medical quality drugs were used The CI 744 was a donation from Dr C C Beck of Parke Davis & Co Ann Arbor Michigan

Results

I FACILITY

1 Minimal subsensitivity of facility response following discontinuous pilocarpine treatment over 11–15 days

Table I shows results of an experiment from June 1966 Twelve adult vervet monkeys previously untreated not iridectomized of both sexes body weight

Table I

Lack of subsensitization by ordinary eye drop treatment One eye treated three times daily for 11–15 days with 1 drop of 2 % pilocarpine Effects of 20 mg/kg hexamethonium (C 6) im and of 20 μg pilocarpine into the anterior chamber following the ganglionic blockade 12 vervets Experiments of 1966

Facilities in μl min^{-1} $mmHg^{-1}$

	Starting facility	Facility drop after C 6	Facility rise after pilocarpine
Treated mean	0.469	0.198	1.33
SEM	0.058	0.033	0.22
Control mean	0.54	0.147	1.54
SEM	0.10	0.028	0.18
Control treated mean	0.076	0.019	0.17
SEM	0.064	0.030	0.19

2.75–4.7 kg were given 1 drop of 2 % pilocarpine HCl into the right eye around 8 a m 2 p m and 6 p m After 11–15 days of unilateral treatment at 6 p m on the day before the facility measurement both eyes received the same dose Next day facility was determined by anterior chamber perfusion First a resting facility was measured then the ganglia were blocked by 20 mg/kg hexamethonium bromide (C 6) finally 20 μg pilocarpine HCl was injected into the anterior chamber Individual facility values and their differences were statistically treated The table shows that there was no significant difference between the two eyes

2 Marked subsensitivity of facility response following continuous pilocarpine treatment for 5–6 days

Fig 2 shows results of 3 experiments in 2 previously untreated cynomolgus monkeys not iridectomized treated with 33 μg pilocarpine/h and challenged with 1 mg/kg pilocarpine iv an almost maximally effective dose in the vervet (Barany 1967)

In panel A the treated eye had worn its insert for 6 days ending 30 min before anterior chamber perfusion was started There was definite miosis Resting facility was higher on this side but it failed to increase when 1 mg/kg pilocarpine was given intravenously The control eye showed a marked re

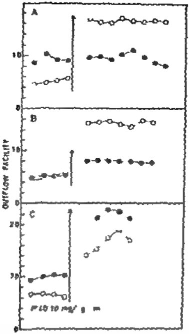


Fig 9

Outflow facility response to pilocarpine in cynomolgus eyes treated with 33 μg/h of pilocarpine for several days Open circles control eye solid circles treated eye A Monkey 450 75 Treatment time 6 days treatment stopped 30 min before start of perfusion Intravenous challenge by 1 mg/kg pilocarpine given over 1 min B Monkey 448 75 Treatment time 5 days In all other respects same as A C Same monkey as in B but 23 days later Challenge by 1 mg/kg pilocarpine im Time interval between individual points 4 min between injection and next point 12 min

sponse In panel B the monkey had worn the insert for 5 days and had it removed 1/2 h before anterior chamber perfusion There was a little miosis Starting facilities were very similar in the two eyes but the response to systemic pilocarpine was much less on the treated side Panel C shows the *same monkey as panel B but 23 days later Starting facility* was higher in the ex treated eye but differences between the eyes are frequently seen in second or later anterior chamber perfusions The important point is that the two eyes now reacted with the same facility increase to systemic pilocarpine sensitivity had recovered

Similar observations were made in a few more facility experiments but since daily facility measurements by anterior chamber perfusion are impossible and since virtually all of the facility effect of pilocarpine is due to ciliary muscle contraction (*Kaufman & Barany 1976a b*) *the rest of the study* was done with accommodation as the measure of ciliary muscle response

II ACCOMMODATION

Before the animals were used in an accommodation experiment they were examined with the slitlamp and ophthalmoscope Already 2 weeks after irid ectomy (the eyes were not treated with autonomic drugs) the media were clear and very little if any signs of intraocular irritation remained At most there remained a patch of fibrin on the anterior lens surface

1 Response of accommodation to pilocarpine or carbachol in totally iridectomized cynomolgus eyes

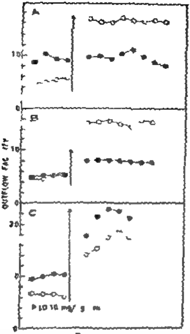
a *Systemic pilocarpine*

In 21 cynomolgus monkeys a standard dose of 1 5 mg/kg pilocarpine was given im divided between 2 sites at about weekly intervals starting 2–3 weeks after iridectomy Table II shows that there was a tendency for the accommodative response to increase with time and the coefficient of variation to decrease the eyes reacted better and more uniformly after the first few weeks This probably represents , quietening down of the eyes after operation There were large consistent differences between animals however (Fig 3) and also consistent but smaller differences between the two eyes (Fig 4)

Table II

Refraction changes (diopters) in 21 totally iridectomized cynomolgus monkeys following 1 5 mg/kg pilocarpine im R = right eye L = left eye

	Weeks between test and iridectomy operation							
	2		3		4		5	
	R	L	R	L	R	L	R	L
Mean	10 07	9 74	9 61	9 48	11 60	11 62	12 64	12 68
SEM	1 18	1 23	1 36	1 32	1 10	1 12	1 12	1 15
SD	5 41	5 87	6 23	6 05	5 68	5 13	5 13	5 27
100 SD/mean	53 7	60 2	64 9	63 8	49 0	44 2	40 6	41 7
Correlation coefficient	0 95		0 97		0 97		0 96	
Orthogonal regression coefficient	1 08		0 97		1 02		1 03	



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Outflow facility response *to* pilocarpine in cynomolgus eyes treated with 33 μg/h of *pilocarpine for several days Open circles control eye solid circles treated eye* A Monkey 450 75 Treatment time 6 days treatment stopped 30 min before start of perfusion Intravenous challenge by 1 mg/kg pilocarpine given over 1 min B Monkey 448 75 *Treatment time 5 days In all other respects same as A* C Same monkey as in B but 23 days later Challenge by 1 mg/kg pilocarpine im Time interval between individual points 4 min between injection and next point 12 min

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$r = 0.56$ $P < 0.01$ Thus differences between eyes tend to persist but as Fig 4 shows as a rule they are not large

In Table II the coefficient of variation of the refraction response in a single eye is above 40 % What causes this large variability? It could be due to differences between animals or between occasions (e g differences in rate of drug absorption or ability of the eyes to react) In a series of 24 cynomolgus monkeys including those of Table II tested at least one month after irid ectomy the average variance in (diopters) of the single refraction response of the single eye was 23 [illegible] (2 occasions) If one forms the series of differences between the responses of the same eyes on the two occasions one obtains an average variance of 8 47 the contribution of the single eye is half or 4 23 Thus the dominant part of the total variance 23 68 – 4 23 is due to differences between animals The most striking finding of this kind was the consistent very low response to systemic pilocarpine in two animals cyno molgus 29 /6 was tested with 1 5 mg/kg pilocarpine im on 5 occasions starting 2 weeks after iridectomy The responses were right eye 2 45 D (range 1 75–3 5) left eye 1 9 (range 1 25–2 5) One week before the last test with pilocarpine (which showed right 3 5 left 2 5) 50 μg carbachol were put under the contact lenses The resulting accommodation was right 27 left 26 D The second case of this kind was cynomolgus 487 75 It was first tested 20 days after iridectomy and then four times at weekly intervals Average response to systemic pilocarpine 1 5 mg/kg was right 3 30 (1 75–5 25) and left 2 38 (0 5–3 5) The eyes were tested with 10 μg carbachol under the contact lens at two occasions following the last pilocarpine test The result was right 12 25 and 8 25 left 12 25 and 7 0 D This is only a little less than the average response to 10 μg carbachol under the contact lens 13 35 ± [illegible]82 D (SD n = 15) Thus there are animals which react poorly to pilocarpine but not to carba chol prior to subsensitization treatment We shall return to this fact later

Systemic carbachol

As Tornqvist (1967) has shown full accommodation can often not be ob tained with systemic carbachol because the blood pressure lowering effect reduces blood perfusion of the ciliary muscle From Tornqvist s Fig 1 it ap peared that 30 μg/kg carbachol im should still be submaximal and on the rising phase Accordingly this dose was given to 7 iridectomized cynomolgi and the effect compared with that of the immediately preceding pilocarpine experiment Three animals contributed 2 eyes on one occasion 4 animals one eye each but on 2 occasions The average response to 30 μg/kg carbachol was 13 50 D (5 25–19 0) and that to 1 5 mg/kg pilocarpine 11 55 D (5 75–19 5) The

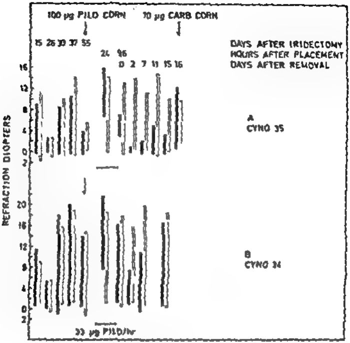

Fig 6

Reduction in accommodation response to pilocarpine after 4 days of continuous pilocarpine treatment by an insert in the conjunctival sac Solid bars experimental eye open bars control eye Lower ends of bars represent starting refraction upper ends the maximum myopia caused by 1 5 mg/kg pilocarpine im or corneal pilocarpine or carbachol First five sets of bars show pretreatment experiments The insert material was leached and released at a constant rate

experiments released 30 μg/h and was leached It was left in the conjunctival sac for 96 h Evidently the subsensitivity to im pilocarpine is more marked than to systemic or topical carbachol

The difference between subsensitivity to pilocarpine *and carbachol already* indicates that unspecific factors cannot be responsible for subsensitivity Before the difference was discovered a small series of blank experiments were made with inserts that had been leached to exhaustion or with carrier rings only Monkeys were given these for 4 days and tested in the usual manner One experiment of this kind is shown as the last pair of bars in Fig 5 B Here the blank treatment evidently had no effect In the animal of Fig 5 A the same experiment was tried but here keratitis developed In 4 other animals the average of the last 2 ratios of pre treatment response experimental control to standard im pilocarpine challenge was 1 04 (0 89–1 1, n = 4) on the day

Table III

Effect of 4 days topical treatment with 30 μg/h pilocarpine on accommodation response to [illegible] μg/kg carbachol im and 1.5 mg/kg pilocarpine im. Figures are ratios between accommodation of treated and control eye. Before treatment ratio is mean of last two before desensitizing treatment. Day of removal of insert is Day 0

Animal	Before treatment Tested with systemic pilocarpine	After treatment			
		Tested with systemic carbachol		Tested with systemic pilocarpine	
		Day 1	Day 3	Day 2	Day 7
32	1.10	0.89	0.73	0.37	
47	1.09	1.14	0.76	0.36	
481	1.09	1.07	0.88	0.47	0.51
482	1.08	0.55[a,b]	0.45	0.23	

[a] Epithelial defect [b] Difficult to read

Table IV

Effect of 4 days topical treatment with 30 μg/h pilocarpine on accommodation response to 10 μg carbachol put onto the cornea and 1.5 mg/kg pilocarpine im. Figures are ratios between accommodation of treated and control eye. Before treatment ratio is mean of last two before desensitizing treatment. Day of removal of insert is Day 0

Animal	Before treatment Tested with systemic pilocarpine	After treatment		
		Tested with corneal carbachol		Tested with systemic pilocarpine
		Day 0	Day 2	Day 1
72	1.04	1.03	0.89	0.60
74	0.98	1.19[a,b]	0.94	0.57[b]
75	1.02	0.94	0.90	0.66
76	0.96	0.96[b]	0.75	0.59[b]

[a] Epithelial defect [b] Difficult to read

of removal of the blank insert 0 89 (0 75–1 11 n = 4) on days 2 or 3 0 90 (0 78–1 0 n – 4) and on day 9 1 02 and 0 86 (n = 2) Thus there may be an effect of irritation causing a loss of accommodation but it is not large if the eye is not strongly irritated

III SUBSENSITIVITY IN THE VERVET MONKEY

All the previous results were obtained in cynomolgus monkeys In order to test if a completely different monkey species behaves similarly a small number of experiments were done in vervets (Cercopithecus ethiops)

The non iridectomized young vervets 296 and 297 were tested 30 μg/kg carbachol im yielded right 16 7 and left 18 1 D in 296 1 0 mg/kg pilocarpine im yielded 18 2 and 18 7 D in 297 Thus the two eyes were quite similar in both monkeys A leached insert releasing 30 μg/h pilocarpine was placed in the right eye of both animals and removed after 4 days On the day after the removal refraction was measured during slowly rising carbachol concen

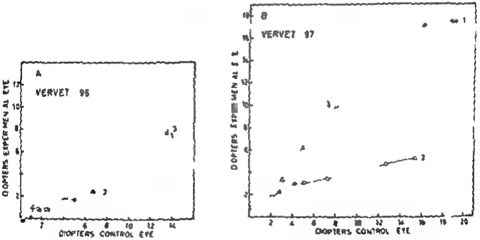

Fig 7

Accommodation caused by gradually increasing concentrations of pilocarpine or carbachol in a normal and a subsensitive eye The experimental eye treated by continuous release of 30 μg h pilocarpine for 4 days from insert in conjunctival sac Non iridectomized young vervet monkeys Tests with 4 × 7 5 μg/kg carbachol im at min intervals on days 1 and 3 after removal of insert and with 4 × 0 25 mg/kg pilocarpine on day 2 (curves numbered accordingly) Duration of run from first injection to maximum accommodation shown

A – 1 24 min 2 1 min 3 14 min

B – 1 19 min 2 16 min 3 9 min

tration instead of giving all of the dose at once 7 5 μg kg was given im every 5 min. Next day 0 25 mg/kg pilocarpine was given im every 5 min instead On day 3 the carbachol schedule was used again Fig 7 A and B shows the results In these plots the accommodation response in the control eye is on the abscissa and that of the treated eye on the ordinate Since the two eyes were not measured strictly simultaneously but sometimes as much as a few minutes apart the values for the control eyes were linearly interpolated to the time for the reading of the experimental eye The limiting factor in these experiments was that the pupils became too small for refractometry *Surprisingly it was the treated pupil that was the smaller both with systemic* carbachol and systemic pilocarpine In monkey 296 only a few readings could be obtained with pilocarpine

The subsensitivity of accommodation on the tested side appears as a slope below 1 0 in the graphs It is evident in Fig 7 B that the subsensitivity was more marked with pilocarpine than with carbachol in fact it is doubtful if there was any subsensitivity for carbachol The reason for the doubt is that

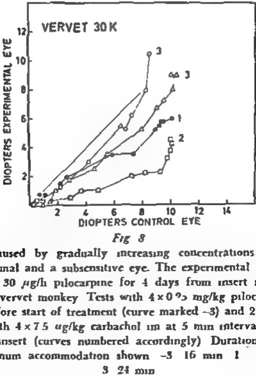

Fig 8

Accommodation caused by gradually increasing concentrations of pilocarpine or carbachol in a normal and a subsensitive eye. The experimental eye treated by continuous release of 30 μg/h pilocarpine for 4 days from insert in conjunctival sac Old iridectomized vervet monkey Tests with 4×0 25 mg/kg pilocarpine im at 5 min interval 3 days before start of treatment (curve marked –3) and 2 days after removal of insert Tests with 4×7 5 μg/kg carbachol im at 5 min intervals on days 1 and 3 after removal of insert (curves numbered accordingly) Duration of run from first injection to maximum accommodation shown –3 16 min 1 6 min 2 24 min 3 24 min

the resting accommodation is not quite stable Presumably accommodative tone could also change during the experiment The exact origin of the curves is therefore uncertain and parallel shifts count less than differences in slope

In one old vervet 30 K iridectomy had been done several years earlier This animal was monkey No 1 in Kaufman & Barany (1975) and in Kaufman & Axelsson (1975) In these experiments the left eye was control the right eye treated with echothiophate for 8 weeks It developed long lasting subsensitivity of accomodation and anterior subcapsular vacuoles The left eye was then treated with atropine echothiophate for 33 weeks (Kaufman & Bárány 1977) It developed no cataract At the time of the present experiments the animal had not been treated for 9 months and the lenses were virtually clear In this case a starting curve was run with repeated pilocarpine injections before the subsensitization treatment (see Fig 8) Most of this curve had slope 1 0 but it showed an upward bend at the end Evidently the control left eye was approaching the maximum of its accommodative ability After subsensitization with 30 µg/h pilocarpine for 4 days in the ordinary manner such a bend was also seen with carbachol as well as pilocarpine The pilocarpine curve again had a much lower slope subsensitivity was more pronounced than for carbachol

Thus in this monkey species too a few days of continuous pilocarpine treatment causes subsensitivity to pilocarpine and also but to a lesser degree to carbachol

Discussion

In the present experiments cholinergic subsensitivity was induced by continuous treatment with pilocarpine Most other work has been done under circumstances where excess acetylcholine was the subsensitizing agent The time course of development of subsensitivity did not obviously differ from that observed in the iris sphincter experiments of Bito and collaborators but the present experiments were not designed to detect other possible differences Instead they came to focus on the remarkable dependence of the degree of subsensitivity on the challenging agent subsensitivity is much more pronounced for pilocarpine than for carbachol Possible explanations will now be discussed

Emmelin (1964 1965) was the first to suggest as a general rule that the sensitivity of the target organ is inversely related to the mean level of transmitter Emmelin s generalization was based on his work with salivary glands in which epinephrine and acetylcholine are both stimulatory After a few days of excess acetylcholine the sensitivity to epinephrine was reduced (*Emmelin*

1964) It certainly appears that *this* subsensitivity could not be due to a change in the cholinergic receptive system However in their review of super and subsensitivity Fleming et al (1973) in order to explain Emmelin s findings tentatively take the position that *all* subsensitivity is a phenomenon beyond the receptors This view is hard to share

Bito (1970 1971) has suggested that muscarinic subsensitivity of the iris sphincter is due to a reduction in receptor concentration on the target cells

Another possibility that has been mentioned (Brodeur & Dubois 1964) but discarded (Perrine & McPhilips 1970) is a reduced affinity of the receptors in the subsensitized tissue

Do any of these explanations of subsensitivity agree with the finding that subsensitivity tested with the partial agonist pilocarpine is deeper than with the full agonist carbachol or are additional assumptions necessary?

1 Reduced affinity of the receptors

Let the affinity between the normally sensitive receptor and the test drug be A and the concentration of the drug C Then fractional receptor occupation is AC/(1+AC) If subsensitivity causes A to become *s*A where $s < 1$ then fractional receptor occupation would be *s*AC/(1+*s*AC) = AC/(1/*s*+AC) Thus the difference between normal and subsensitized is the first term of the denominator 1/*s* or 1 This difference will have more effect on the value of the fraction if AC is small than if AC is large For the same degree of control eye accommodation AC has to be much larger with a partial agonist like pilocarpine than with a high intrinsic activity drug like carbachol Subsensitivity should therefore be more marked with carbachol than with pilocarpine The opposite was observed and reduced affinity of the receptors *per se* is no acceptable explanation of our findings

2 Phenomena beyond the receptor

It is difficult to see how these phenomena could distinguish by which drug the receptor is occupied If excitability were depressed it should make no difference whether the excitant is pilocarpine or carbachol

3 Reduced receptor concentration on the target organ

Whether this could explain the difference between carbachol and pilocarpine needs a lengthier analysis

The relation between excitation of the ciliary muscle and accommodation is not straightforward the shape changes in the lens are several steps removed

from the shape changes of the smooth muscle cells It is possible that in the normal state the zonule relaxes completely before the ciliary muscle has *reached its absolute* maximum of contraction the muscle may have spare contraction The relation between muscle contraction and accommodation is then approximated by Fig 9 A A small threshold contraction is assumed whether it exists is not known

Some kind of relation similar to Fig 9 B must exist between number of receptors occupied by the stimulant drug and ciliary muscle contraction (Note that this is not a dose response curve) For the present purposes it will be approximated by a straight line as in Fig 9 C There is a threshold number a slope and a maximum contraction which with a full *agonist* is the absolute maximum of the muscle Line 1 represents a high intrinsic activity compound like carbachol with ability to cause a maximum contraction without occupying all receptors and line 2 a less efficient but still full agonist Line 3 represents a not quite full agonist assumed to cause at most 85 % of full contraction and line 4 is a more clearly partial agonist perhaps like pilocarpine (Lommatsch 1963) that even at full receptor occupation is unable to cause more than 70 % of maximum contraction In the graphs the number of occupied receptors needed for threshold stimulation by the different drugs is

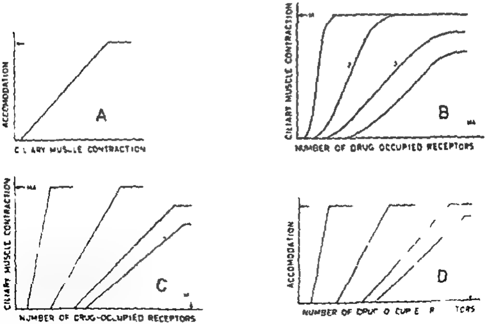

Fig 9 A–D
Explanation see text.

proportional to the number needed for maximum stimulation – this is reasonable but not proven

By combining relations 9 A and 9 C one obtains 9 D the relation between number of receptors occupied and accommodation The lines have different slopes K and thresholds T Note that line 3 representing a partial agonist is still able to cause full accommodation because we have assumed spare contraction

Now assume that the ciliary muscle of the control eye has a total of R receptors all of one kind and that the muscle of the subsensitized eye has lost some and has *s*R with $s < 1$ Call x the proportion of occupied receptors for a given drug concentration then at that concentration the number of occupied receptors is xR in the control and *s*xR in the subsensitive eye Assume that the drug used for testing is that represented by line 1 of Fig 9 D and that we are above threshold but below maximum accommodation as indeed we are in the experiments Then accommodation in diopters D is

$$D_c = K_1 \, (xR - T_1) \text{ for the control eye and}$$

$$D = K_1 \, (sxR - T_1) \text{ for the subsensitized eye}$$

By elimination of xR and rearrangement one obtains

$$D_s = s \quad D_c - K_1 T_1 \, (1 - s)$$

Evidently for drugs represented by lines 2 3 and 4 only K and T will be different

Thus under the assumption of simple receptor loss there is a linear relation between the accommodation response in the subsensitized eye and that in the control eye The slope is *s* and independent of the intrinsic activity of the test drug But we have seen Fig 7 8) that in fact the slope is much less with pilocarpine than with carbachol Thus a simple reduction in one kind of receptors is not sufficient to explain the findings even if partial agonism thresholds spare receptors and spare ciliary muscle contraction are invoked

Bito et al (1971) who similarly found that the response to pilocarpine of the rat iris sphincter *in vitro* was more depressed by subsensitivity than the response to carbachol acetylcholine or metacholine were forced to the suggestion that acetylcholine and pilocarpine act on two different populations of receptors The presence of several kinds of muscarinic receptors in smooth muscle is possible but has not been proved (cf Fisher et al 1976) It seems more likely that the explanation resides in special properties of one of our two test compounds most likely pilocarpine

It is known that pilocarpine is a compound with multiple actions and that it can be auto inhibitory At 10^{-4} M it starts to relax the rat jejunum *in vitro*

by a papaverine like action (van Rossum 1962 Fig 9) In the guinea pig ileum it is already down to half maximum contraction at 10^{-5} M while carbachol under exactly the same conditions becomes equally self inhibitory only at 10^{-1} M (Bown et al 1973 Fig 2) True these phenomena become evident at concentrations too high to be of interest in the present connection but they occur against a background of maximum stimulation If the stimulation were smaller the relaxant effect could conceivably have been already evident at a lower concentration In the cat eye with typical application *in vivo* (Bito & Dawson 1970 Fig 1) even a dose close to the normal threshold for miosis dilates the pupil after subsensitization (carbachol does not) Similar direct observations of a non cholinergic relaxant action on the ciliary muscle are not yet possible since we *still have no way to stimulate the muscle non cholinergically*

If we assume then that in the ciliary muscle also pilocarpine exerts opposing actions of not very dissimilar size contracting by a muscarinic and relaxing by a different mechanism both already coming into play at the low concentrations present in our experiments then the difference in subsensitivity between pilocarpine and carbachol would be explained Since cholinergic subsensitivity would affect only the stimulant action the net effect of the two opposing actions would decrease faster with developing subsensitivity than that of carbachol which lacks the non cholinergic relaxant effect

If this hypothesis is correct the difference between pilocarpine and carbachol cannot be held against any of the explanations of subsensitivity mentioned at the start of the Discussion A composite action would also make it easier to explain the large interindividual sensitivity differences to pilocarpine with occasional occurrence of almost insensitive individuals In these the opposing actions would nearly balance Similarly this concept leaves room for interspecies differences

The clinical implications of the present findings are not quite clear Undoubtedly the basic phenomenon of cholinergic subsensitivity will be found in the human eye too In the eye drop experiments the night interval between drops was 14 h much longer than in clinical practice This may well explain why no subsensitivity was seen It is probable that all treatment regimens involving the presence of cholinergic stimulation most of the time will produce some degree of subsensitivity of the ciliary muscle but whether or not this is clinically relevant may depend on the drug The cholinesterase inhibitors potentiate acetylcholine so much that their action on the ciliary muscle can be upheld despite subsensitivity (Kaufman & Bárány 19 ?) A direct acting drug like carbachol may elicit subsensitivity of the muscle but

conceivably not more than can be overcome – this will have to be tested The problem drug is pilocarpine In terms of the dual action concept what is the relation between stimulant and relaxant action in the human ciliary muscle and in the individual patient? A patient with little relaxant action would tend to react favourably already to the first drop of pilocarpine and would become only moderately subsensitive during continued treatment The other extreme would be a case that shows little facility increase with pilocarpine (because of the large relaxant component) and who reacts better to other miotics

But even if patients were to lose the facility effect of pilocarpine they still may derive benefit from the drug As stressed especially by Krill & Newell (1964) pilocarpine can produce a definite lowering in ocular tension without an increase in facility of outflow A direct depressing effect of pilo carpine on secretion by the ciliary processes of rabbits was demonstrated by Berggren (1965) *In vivo* reduction in aqueous formation was demonstrated in monkey experiments by Bill & Wålinder (1966) and Wålinder & Bill (1969) and in healthy human volunteers by Gasterland et al (1975) The last men tioned authors also found an increase in pseudofacility Thus the reasons for the proven clinical efficiency of continuous or semicontinuous pilocarpine can be several and probably differ between individual patients But among the reasons for therapeutic failure with such a pilocarpine regimen subsensitivity may play a role

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References

Auricchio G & Diotallevi M (1959) Sulla azione dei farmaci parasimpaticosimili diretti ed indiretti sullo sfintere irideo del coniglio *Ann d'Ottalm e Clin Ocul 85* 529–533

Barany E H (1966) Doyne memorial lecture The mode of action of miotics on out flow resistance A study of pilocarpine in the vervet monkey Cercopithecus ethiops *Trans ophthal Soc U K 86* 539–578

Bárány E H (1967) The immediate effect on outflow resistance of intravenous pilo carpine in the vervet monkey Cercopithecus ethiops *Invest Ophthalmol 6* 373–380

Berggren L (1965) Effect of parasympathomimetic and sympathomimetic drugs on secretion in vitro by the ciliary processes of the rabbit eye *Invest Ophthalmol 4* 91–97

Berggren L & Wålinder P E (1969) Tonus of the ciliary muscle during sleep *Acta ophthal (Kbh) 47* 1149–1155

Bill A & Wålinder P E (1966) The effect of pilocarpine on the dynamics of aqueous humor in a primate (Macaca irus) *Invest Ophthalmol 5* 170–175

Bito L Z (1968) The absence of sympathetic role in anti ChE induced changes in cholinergic transmission *J Pharmacol exp Ther 161* 302–309

Bito L Z & Banks N (1969) Effects of chronic cholinesterase inhibitor treatment I The pharmacological and physiological behavior of the anti ChE treated monkey (Macaca mulatta) iris *Arch ophthal (Chicago) 82* 681–686

Bito L Z & Dawson M J (1970) The site and mechanism of the control of cholinergic sensitivity *J Pharmacol exp Ther 175* 673–684

Bito L Z Dawson M J & Petrinovic L (1971) Cholinergic sensitivity normal variability as a function of stimulus background *Science 172* 583

Bito L Z Hyslop K & Hyndman J (1967) Antiparasympathomimetic effects of cholinesterase inhibitor treatment *J Pharmacol exp Ther 157* 159–169

Bown F Graham J D P & Taha S A (1973) Fade and desensitisation in guinea pig ileum and vas deferens *Europ J Pharmacol 22* 64–74

Brodeur J & Dubois K P (1964) Studies on the mechanism of acquired tolerance by rats to O O diethyl S 2 (ethylthio)ethyl phosphorodithioate (Di syston) *Arch int Pharmacodyn 149* 560–570

Emmelin N (1964) Action of acetylcholine on the responsiveness of effector cells *Experientia 20* 275

Emmelin N (1965) Action of transmitters on the responsiveness of effector cells *Experientia 21* 57–65

Fisher A Grunfeld Y Weinstock M Gitter S & Cohen S (1976) A study of muscarinic receptor heterogeneity with weak antagonists *Europ J Pharmacol 38* 131–139

Fleming W W McPhillips J J & Westfall D P (1973) Postjunctional supersensitivity and subsensitivity of excitable tissues to drugs *Ergebn Physiol 68* 55–119

Gaasterland D Kupfer C & Ross K (1975) Studies of aqueous humor dynamics in man IV Effects of pilocarpine upon measurements in young normal volunteers *Invest Ophthalmol 14* 848–853

Kaufman P L & Axelsson U (1975) Induction of subcapsular cataracts in aniridic vervet monkeys by echothiophate *Invest Ophthalmol 14* 863–866

Kaufman P L & Bárány E H (1975) Subsensitivity to pilocarpine in primate ciliary muscle following topical anticholinesterase treatment *Invest Ophthalmol 14* 302–306

Kaufman P L & Barany E H (1976a) Residual pilocarpine effects on outflow facility after ciliary muscle disinsertion in the cynomolgus monkey *Invest Ophthalmol 15* 558–560

Kaufman P L & Bárány E H (1976b) Loss of acute pilocarpine effect on outflow facility following surgical disinsertion and retrodisplacement of the ciliary muscle from the scleral spur in the cynomolgus monkey *Invest Ophthalmol 15* 793–807

Kaufman P L & Barány E H (1974) Subsensitivity to pilocarpine of the aqueous outflow system in monkey eyes following topical anticholinesterase treatment *Amer J Ophthal* in press

Kaufman P L & Lutjen Drecoll E (1975) Total iridectomy in the primate in vivo surgical technique and postoperative anatomy *Invest Ophthalmol 14* 766–771

Krill A E & Newell F W (1964) Effects of pilocarpine on ocular tension dynamics *Amer J Ophthal 57* 34–41

Lommatzsch P (1963) Über Versuche mit Pilokarpin am isolierten Ciliarmuskel und Sphincter iridis *Albrecht v Graefes Arch Ophthal 165* 457–494

Perrine S E & McPhillips J J (1970) Specific subsensitivity of the rat atrium to cholinergic drugs *J Pharmacol exp Ther 175* 496–507

Tornqvist G (1967) Accommodation in monkeys Some pharmacological and physiological aspects *Acta ophthal (Kbh) 45* 1–52

Van Rossum J M (1962) Pharmacodynamics of parasympathetic drugs Mechanism of action and structure action relationship of tertiary ammonium salts *Arch int Pharmacodyn 140* 592–605

Wålinder P E & Bill A (1969) Influence of intraocular pressure and some drugs on aqueous flow and entry of cycloleucine into the aqueous humor of vervet monkeys (Cercopithecus ethiops) *Invest Ophthalmol 8* 446–458

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LENTICONUS IN ALPORT'S SYNDROME

A Family Study

BY

D S SINGH D B BISHT SHASHI KAPOOR B N SHARMA
K SANKARAN and N K MAJUMDAR

A South Indian family with three well documented cases of Alport's syndrome with anterior lenticonus are reported Clinical features of the syndrome including ocular and laboratory findings have been presented and discussed Macular pigmentation 2 cases subcapsular opacity and nephrotic syndrome one case each observed in the present series are of great interest and are quite rare in patients with Alport's syndrome Critical analysis of the family pedigree revealed autosomal dominance with incomplete penetrance as the possible mode of genetic transmission of the disease

Key words Alport's syndrome – lenticonus – hereditary nephritis – neuro sensory deafness – nephrotic syndrome – haematuria

The presence of anterior lenticonus forms a significant clue to the diagnosis of systemic disorders such as hereditary nephritis and deafness constituting Alport's syndrome Arnott et al (1966) collected 12 cases of Alport's syndrome with anterior lenticonus since then a few more reports have appeared stressing this association (Crawfurd & Toghill 1968 Shani & Fine 1970 Purriel et al 1970) The ocular abnormalities apart from lenticonus described in these cases were arcus juvenilis (Chavis & Croshong 1973) rupture of anterior lens capsule (Ehrlich 1946) subcapsular cataract (Goldbloom et al 1957) sphero

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phakia (Sohar 1956 Goldbloom et al 1957) pigment dispersion syndrome (Davies 1970) and heterochromia of the iris (Kapoor 1976) Retinochoroidal lesions like choroidal atrophy (Sohar 1956) drusen of the disc (Friedburg 1968) macular pigmentation (Perrin 1962) and detachment of retina (Williamson 1961) have also been reported

The purpose of the present communication is to report a family of Alport's syndrome where anterior lenticonus and macular pigmentation were prominent features Heterochromia of the iris was present in one case (Pedigree IV–4) and cornea guttata in two cases (Pedigree IV–1 & 4) – one of our patients (Pedigree IV–3) presented with nephrotic syndrome which is a rare manifestation of the disease (Knepshield et al 1968)

Case Reports

(Pedigree IV–3) A 17 year old male resident of Salem was admitted to a medical ward with puffiness of the face distension of the abdomen and progressive oliguria for 15 days The patient was a young well built male He had moderate pallor puffiness of the face and bilateral paedal and subcutaneous oedema The blood pressure was 1[illegible]0/100 mmHg and jugular venous pressure was elevated

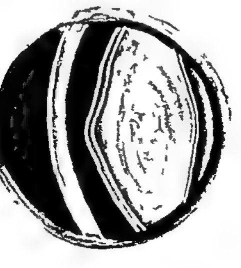

Fig 1
Schematic representation of anterior lenticonus

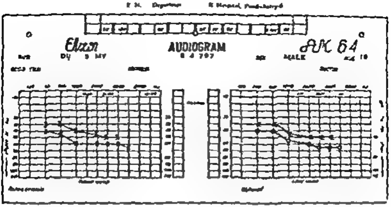

Fig 2
Audiometry of the patient (Pedigree IV-3) showing neurosensory deafness

Systemic examination revealed a bilateral pleural effusion. The liver was palpable 5 cm below the right costal margin and was soft smooth and slightly tender Examination of the cardio vascular system was normal Laboratory findings included haemoglobin 10 g/100 ml and 24 h urinary protein of 4 5 g Detailed urine analysis revealed microscopic haematuria with 15 to 20 RBC per high power field Blood urea ranged from 166 to 250 mg/100 ml Serum creatinine was 4 mg 100 ml Serum cholesterol was 350 and 500 mg/100 ml on two occasions

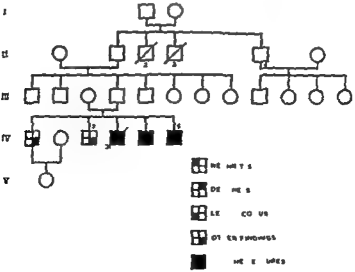

Fig 3
Pedigree of Alport s syndrome family with anterior lenticonus and nephrotic syndrome

The patient was diagnosed as a case of chronic renal failure due to nephrotic syndrome The fundus was examined for uraemic changes but its appearance was not very clear Hence the case was referred for an ophthalmologist's opinion

The ocular examination showed bilateral anterior lenticonus (Fig 1) and macular pigmentation The visual acuity was 6 60 in both eyes which was not correctable with glasses On direct interrogation the patient gave a history of progressive deafness since childhood Audiometry revealed a sensory neural deficit (Fig 2) On the basis of renal ocular and auditory findings the diagnosis was changed to that of Alport's syndrome

A detailed family history was recorded and examination of the other members of the pedigree IV was carried out It indicated the involvement of two younger bothers (Pedigree IV-4 & 5) Two members (Pedigree II-3 & 4) died below the age of 20 years due to an illness suggestive of chronic renal failur (Fig 3) They might also have suffered from Alport's syndrome

The detailed clinical ocular and biochemical findings of the family members of pedigree IV are presented in Table I

Table I

Clinical features in asymptomatic members of pedigree IV

Clinical features		Pedigree numbers			
		1	2	4	5
Age		27	23	15	13
Sex		Male	Male	Male	Male
Haematuria		–	–	++	++
Haemoglobin (g/100 ml)		14 5	13 0	12 0	11 5
Albuminuria		–	–	++	++
Twenty four hours urinary protein (g)		–	–	–	–
Blood urea (mg/100 ml)		27	20	23	20
S creatinine (mg/100 ml)		0 8	1 2	2 0	1 8
S cholesterol (mg/100 ml)		130	166	125	148
Deafness		–	–	+	+
Anterior lenticonus		–	–	+	+
Macular pigmentation		+	+	+	+
Anterior subcaps cataract		+	–	–	–
Heterochromia of the iris		–	–	+	–
Cornea guttata		+	–	+	–
Visual acuity	R	6/6	6/6	5/9	6/18
	L	6/6	6/6	6/9	6/18

Discussion

Anterior lenticonus is a rare anamoly of the lens where the anterior curvature is markedly increased in its axial part An oil globule reflex opposite a normal fundus glow indicates lenticonus in the absence of keratoconus Its association with Alport s syndrome is believed to be the result of defective development of the lens or its capsule (Mann 1957 Duke Elder 1964) or of the metabolic defects of Alport s syndrome (Arnott 1966)

The other ocular findings in the present series were dense macular pigmentation (in all the members of Pedigree IV) heterochromia of the iris *(Pedigree IV–4)* and *cornea guttata (Pedigree IV–1) Anterior subcapsular* cataract was not seen in any of the cases with anterior lenticonus however it was present in another case (Pedigree IV–1) who had no other features of Alport s syndrome

Dense macular pigmentation though of little consequence as evidenced by normal visual acuity in cases 1 and 2 of Pedigree IV is a significant finding It cannot be taken as a normal phenomenon because of the young age of the subjects under study Moreover it cannot be regarded as a part of Alport s syndrome as other essential features of the disease such as nephritis and deafness were absent in these cases but whenever it is seen in cases with Alport s syndrome it has been considered as a part of a pigment dispersion syndrome (Davies 1970) Heterochromia of the iris can also be considered as a part of the same syndrome

The subcapsular opacities in Alport s syndrome have aroused great con*troversy regarding their pathogenesis A congenital defect in the development* of lens (Mann 195) rupture in the anterior capsule (Ehrlich 1946) and stretch on the anterior pole of the lens (Kapoor 1976) have been suggested None of *our cases of Alport s syndrome had subcapsular opacities* however they were present in one case (Pedigree IV–1) who had no other features of the syndrome This leads us to believe that the subcapsular cataract is a type of congenital cataract independent of the pathology of Alport s syndrome

Various functional renal changes in Alport s syndrome are haematuria and proteinuria in males and pyuria in females Urine analysis and biochemical findings in those cases are suggestive of chronic glomerulonephritis (Kaufman et al 19 0 Purriel et al 1970) One of our patients (Pedigree IV–3 had features of the nephrotic syndrome which is rarely seen in patients with Alport s syndrome (Knepshield et al 19(S)

The morphological lesions in the kidney are minimal and non specific during the early stages of the disease (Perkoff et al 1958 Keyersbach & Butler 1954) Detailed studies at various stages of the diseases have shown features

suggestive of chronic glomerulonephritis (Krickstein et al 1966 Kaufman 1970) Recent electron microscopic studies have demonstrated thickening of glomerular basement membrane with splitting and splintering of lamina densa in a focal and local fashion (Hinglais et al 1972 Churg & Sherman 1973) These changes are now considered as early and specific renal lesions of Alport's syndrome

The exact mode of inheritance of Alport's syndrome is not known The possible mode of genetic transmission is autosomal dominant with differential penetration (Perrin 1962) or with sex linked suppressor gene in females (Friedburg 1968) The present family does not give a clear indication regarding its mode of transmission because only one pedigree could be examined However it appears to be more in favour of an autosomal dominant transmission with incomplete penetrance

References

Alport A C (1927) Hereditary familial congenital haemorrhagic nephritis *Brit med J 1* 504–506

Arnott E J Crawfurd M D A & Toghill P J (1966) Anterior lenticonus and Alport's syndrome *Brit J Ophthal 50* 390–403

Chavis R M & Groshong T (1973) Corneal arcus (arcus juvenilis) in Alport's syndrome *Amer J Ophthal 75* 793–794

Crawfurd M D A & Toghill P J (1968) Alport's syndrome of hereditary nephritis and deafness *Quart J Med 37* 563–576

Churg J P & Sherman R L (1973) Pathologic characteristics of hereditary nephritis *Arch Path 95* 374–379

Davis P D (1970) Pigment dispersion in a case of Alport's syndrome *Brit J Ophthal 54* 557–561

Duke Elder S (1964) *System of Ophthalmology* Vol 3 pp ? & 69 Kimpton London

Ehrlich L H (1946) Spontaneous rupture of the lens capsule in anterior lenticonus *Amer J Ophthal 29* 1274

Friedburg D (1968) Pseudoneuritis and drusenpapillebeins Alport syndrome Deformation of Auricle *Klin Mbl Augenheilk 159* 379

Goldbloom R B Fraser F C Waugh D Aronovitch M & Wiglesworth W F (1957) Hereditary renal disease associated with nerve dafness and ocular lsions *Pediatrics 20* 241–252

Hinglais N Grunfeld J P & Bois E (1972) Characteristic ultrastructural lesion of glomrular basement membrane in progressive hereditary nephritis *Lab Invest 27* 473–487

Kapoor S & Sood M (1976) Anterior lenticonus in a case of Alport's syndrome *Eye Ear Nose Thr Mon* (in press)

Kaufman D B McIntosh R M Smith F G Jr & Vermier R L (1970) Diffuse familial nephropathy a clinico pathological study *J Pediat 77* 37–47

Knepshield J H Robert I L Davis J & Moser H (1968) Hereditary chronic nephritis complicated by nephrotic syndrome *Arch intern Med 12* 156-158
Krickstein H I Gloor F J & Balogh K I (1966) Renal pathology in hereditary nephritis with nerve deafness *A M A Arch Path 8*" 506-517
Mann I (1957) *Developmental abnormalities of the eye* IInd ed pp 298-311 Lippincott Philadelphia
Perkoff G T (1967) The hereditary renal diseases *New Engl J Med 2 7* 79-85
Perkoff G T Nugent C A Jr Dolowitz D A Stephens F E Carnes W A & Tyler F H (1958) A follow up study of hereditary chronic nephritis *Arch intern Med 102* 733-746
Perrin D (1962) Contribution a l etude du syndrome nephropathie familiale surdité malformations oculaires Thesis Paris
Purriel P Drets M Pascale E Cestau R S Borras A Ferreira W A Lucca N D & Fernandez L (19 0) Familial hereditary nephropathy (Alport s syndrome) *Amer J Med 49* 753-773
Reyersbach G C & Butler A M (1954) Congenital hereditary haematuria *New Engl J Med 251* 3 7-380
Sham M & Fine L G (1970) Hereditary nephritis and deafness *Israel J med Sci 6* 544-548
Sohar E (1956) Renal disease inner ear deafness and ocular changes A new heredo familial syndrome *Arch intern Md 9* 627-630
Williamson D A J (1961) Alport s syndrome of hereditary nephritis with deafness *Lancet 2* 1321-1323

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Nils Christensen Ocular Malformation induced by Radiation of the Mouse Embryo Copenhagen 19/6 F A D L 1/0 pages 95 photomicrographs Price D Kr 42

Microscopic studies of radiation induced malformations have been performed only to a limited extend before This Danish thesis gives a detailled systematic investigation of the radiation induced defects compared with a control group comprising a total of 44 000 histological sections of mouse embryos

Severe defects comprised anophthalmia and rudimentary eyes microphthalmia with uveal coloboma retinal eversions retinal folds medullary epithelium in the pigment epithelium eosinophilic structures hypoplastic changes of the lids anterior lenticonus with lens fibres embedded in the corneal stroma keratinization of the cornea etc

Mild defects comprised proliferation of vitreal vessels coloboma of the disc lens vacuoles etc Most of the defects were stage specific (in a specific time of the gestation period) but not dose specific Some unilateral defects occurred in a higher incidence on the right eye others on the left eye The majority was bilateral

The book comprises sections concerning retinal dysplasi in mice the embryonic development of the mouse eye conclusions legends and symbols to the figures table captions index and 8 pages of references

The reproductions of the photomicrophotographs are not of the highest quality but the fair copy for offset reproduction is exellent

The book is to be recommended for all interested in congenital diseases and defects

M S Norn

H J Merté Augenartzliche Fortbildung Jahreskurse fur die praktische Augenheil kunde Bd 4 Teil 2 Urban & Schwarzenberg Munchen 19 6 pp 135–278 DM 40 –

This second volume contains eight papers on binocular vision in children a discussion on the possibilities of treatment and prophylaxis of axial myopia and a final presenta tion of colour vision and its disturbances

The interest in examination of children and in early diagnosis of squint has been increasing in recent years and the present collection of papers may serve as an intro duction but also as an incitement Papers are short and concise the book is lightweight

The chapter on possibilities and limits in the treatment and prophylaxis of axial myopia would seem to be an excellent review The last chapter also is a recommendable presentation of colourvision problems

This volume seems to be of a particular interest to practising ophthalmologists

Niels Ehlers

Charles D Kelman Phacoemulsification and Aspiration The Kelman Technique of Cataract Removal Aesculapius Publishing Company Birmingham Alabama (1976) 152 pp 240 illustrations and 16 colour photographs Price Dfl 136 00

Even though intracapsular cataract operation is one of the most successful of all operations it is not without its complications Therefore any technical improvement which is able to reduce the operative risks shorten the period of hospitalisation and lessen the number of complications is to be welcomed

Dr Kelman's new technique is based on the idea that the main complication lies in the cataract incision and that it should therefore be possible to lessen the complications by reducing the size of this opening A ventilated cystotome is first introduced through this incision and the capsule is opened and the nucleus luxated forwards into the anterior chamber This is then followed by the phacoemulsificator which by means of ultrasonic oscillations is able to disintegrate the lens nucleus and aspirate it at the same time

The format of the book is rather large and bulky It is very well illustrated not only with excellent drawings but also with coloured photographs The illustrations take up more space that the whole of the text The book is intended to be a supplement to a course on phacoemulsification With its step by step layout the book is written for the beginner However it is the author's opinion that the technique should not be used until a sound operative background has been acquired – not least with the operating microscope

The author gives a thorough account of all his experiences with the development of the method and refers in such detail to the first trials and procedures which were later shelved as to make the book appear somewhat disproportionate

The major part of the book is naturally enough concerned with the technical description of the apparatus together with the operative technique There can be little doubt that the performance of such a refined operation demands considerable training and technical ingenuity Inside the anterior chamber tightly confined between the corneal endothelium and the hyaloid membrane must be like finding oneself between Scylla and Charybdis

However ingenious this new operating technique is the most interesting fact is not the technical data but the indication for its use As far as one is able to judge from the book the indication not for aspiration which has been known for some time but for phacoemulsification comprises certain congenital cataracts and presenile immature cataracts It would be interesting to know how satisfactory the results are in this group

Even though the author states that 45 000 operations have been performed using this technique naturally enough successfully it is a little disappointing to find that there is no mention of any analysis of the results There is no doubt that this new technique has its place However before one can consider trying this expensive and technically difficult method a convincing documentation of the suitability not to mention superiority of the method over the highly successful conventional cataract operation must be made available

The cover of the monograph contains the following words the most innovative development of cataract surgery in this century

The future will show whether these promising words can be borne out

J Edmund

W D Schafer Strabismus in der Praxis Untersuchungstechnik und Behandlungsablauf Springer Verlag Berlin 1976 137 pages Price 18 80 DM

The author is head of the Strabism Clinic in the University Eye Clinic Department Wurzburg West Germany

This little pocket sized book covers examination techniques orthoptic and pleoptic treatments with special attention to prism therapy in cases of anormal retinal correspondence sections concerning penalisation bifocal spectacles common errors and damages of wrong treatment etc

The book is concluded with a list of definitions of German strabismologic words

The book can be recommended to orthoptists and ophthalmologists as an unshaded short instruction in ortoptic examination and therapy

M S Norn

Kurt A Gitter Current concepts of the vitreous including vitrectomy The C V Mosby Company Saint Louis 1976 289 pp 271 ill Price $ 33 10

In recent years interest in the corpus vitreum has increased especially following the introduction of vitrectomy instruments This has manifested itself in an increasing number of symposia on the corpus vitreum involving discussions on anatomy histochemistry pathology and not least on the surgery of the corpus vitreum

This book is one of a series of such symposia in which the latest instruments and their respective advantages and the preliminary experiences from their use are discussed

At the present time a considerable selection of instruments are available all of which are based on the original instruments of Robert Machemer There can hardly be any doubt that vitrectomy via the pars plana is an operation that has come to stay but its proper place has yet to be established

The experience to date with this time consuming technique appears to indicate that both the anterior and the posterior segments will come to benefit from this operative method – that is assuming the operation be performed by an experienced surgeon

This sound and interesting account however conveys nothing new to those who have followed the development of corpus vitreum surgery from the beginning

Jens Edmund

Everett R Veirs Lacrimal disorders diagnosis and treatment C V Mosby Comp Saint Louis 1976 179 pp 183 ill Price $ 25 75

The author emphasizes that a normal lavage of the lacrimal system is not always identical with a normal function of the lacrimal system He advises several methods of examination of great value in general practice

The dye passage to the nose the lacrimal river dilution test the rose bengal vital staining examination of the movement of the lacrimal punctum by blinking function of the common cannaliculus (tendency for lavage fluid to leave through the other punctum) etc

He mentions the considerable variations in the results of the Schirmer test (7-70 mm in dry eyes)

The break up time (wetting time) discussions concerning paradoxical epiphora and reflectory diminished tear production by diminished tear outflow are not included

In some cases he treats hypersecretion by cauterisation of the ductules from the *lacrimal gland but the results are unpredictable*

He stresses the importance of a functioning round punctum lacrimale and advises a triangular cut to open the vertical canaliculus in an ectropionized or a closed punctum never creating a slit in the horizontal canaliculus

He treats the narrow common canaliculus with his stainless canalicular rod sutured to the skin of the eyelid (Ethicon 03 G)

There is a chapter dealing with dacryocystography which contains many good illustrations

Another chapter describes external dacryocystorrhinostomy in detail The author *underlines that it is totally unnecessary to sever the medial palpebral tendon in this* operation that the success rate approximates 100% and pyrex glass tubes or skin grafts are only necessary in the most complicated cases

He describes conjunctivodacryocystorrhinostomy with lacrimal or nasal mucosa and *reconstructive surgery with canalicular rod or Worsts pigtail probe*

Emi scanning technetium lacrimal scanning and ultrasonography are only briefly mentioned

The book is of a high standard characteristic for the Mosby series with large in*structive black and white photographs The text is of special interest for the ophthalmic* practitioner with descriptions of the most important methods of examination for office use The text is based more on the authors considerable clinical experience than on references from the literature

The book is to be recommended for all those interested in a rational treatment of lacrimal disorders – ophthalmic practitioners as well as lacrimal surgeons

H S Sorn

3 *Delmarcelle J François F Goes J Collignon Brach J Luyckx Baeus C H Verbraeken* Biometrie oculaire clinique (Oculometrie) Masson Paris 19 6 608 p (116 tables 191 figures)

The present book deals with that part of ophthalmology in which mere qualitative clinical impressions may be quantified through exact measurements

The initial 40 pages are devoted to considerations about measurements and their interpretation including a summary review of basic statistics

The second part (300 pages 10 chapters) deals with the normal ocular biometry It is a discussion of the many techniques available and the socalled norms in healthy eyes with *special reference to the influence of age and refraction Separate chapters* deal with orbit eye size (axial length volume) cornea lens iris anterior chamber ocular fundus (optic nerve head in particular) correlations and refraction

In the third part (150 pages 5 chapters) various disease entities are analysed from an oculometric point of view among them the composite field of glaucoma Without adhering to a strictly one sided oculometric concept (e g angle closure glaucoma is

not explained *only* by dimensional parameters) a great many findings are collected and presented A certain amount of overlapping is inevitable especially where the same findings are referred to and discussed in part 2 as well as in part 3

Some items have got many pages viz the minute analyses of the height of the corneal dome as related to lens position and thickness limbic position corneal curvature radius etc apparently fields of special interest to some of the authors Other subjects are merely included for the sake of completeness e g the variations in interpupillary distance There is no definition of hyper and hypotelorism and normal values are not given Further I was a little embarassed to find a review of the effects of recession/resection/myotomy of the external eye muscles Probably other books will be consulted by the squint surgeon

The six Belgian authors need no further presentation They are all known from (inter alia) a great number of oculometric papers also including ultrasound studies The prosperous results of ultrasound oculometry – here added to the information derived from the optical techniques – have undoubtedly been the inspiration behind the present book

With only a scant 1900 references covering the period up to 1976 the book can not be complete Some of the conclusions have already been modified Thus a decreasing central corneal thickness with age and the prematurely born children s lack of catching up in eye size are still more recent findings Indeed this illustrates that clinical oculometry is a vivid field of research

The book will be used as an oculometric Duke Elder In spite of some heterogeneity it is warmly recommended to any ophthalmologist occupied with the significance of eye dimensions for ocular function and disease (and should not we all be?) Further ophthalmic libraries can not be without this the first basic book in clinical oculometry

Hans Fledelius

David D Donaldson Atlas of Diseases of the anterior segment of the eye Volume V The crystalline lens Mosby Saint Louis 1976 209 pages 199 illustrations 112 stereoscopic view in full colour on 16 View Master® reels and a View Master® compact viewer Price $ 57 95

Volume V in the highly valued series Atlas of diseases of the anterior segment of the eye by Donaldson concerns the lens and includes the following chapters Anatomy and embryology anomalies and capsulolenticular abnormalities congenital and sutural cataract presenile and senile cataracts and pseudoexfoliation of the lens capsule cataracts in systemic and ocular disorders traumatic cataracts and dislocation of the lens radiation, electric shock and toxic cataracts iatrogenic surgical complications

As a stereoscopic impression is essential to the understanding of the morphology of the lens a study of the 112 stereoscopic views provides an important and new feature for students and ophthalmologists A portable folded viewer is provided but a cheap battery viewer is better and far more comfortable It is quite possible to show the stereoscopic slides to a large audience by means of a View Master projector and polarised glasses The accompanying text and the short case histories cover the material in an ideal way

P Brændstrup

VARIA

XXIII International Congress of Ophthalmology

will be held May 14-20 1978 in Kyoto Japan

The scientific program covers main reports concerning ocular immunology retinal pigment epithelium round table discussions concerning ocular toxicology choroidal circulation corneal diseases optic neuropathy pathology of visual cells vitreous surgery and infections Further free papers and symposia (International Organization against Trachoma International Agency for Prevention of Blindness International Study Committee for Teaching Post graduate Continuing Education in Ophthalmology and International Glaucoma Club)

Inquiries : Secretariat XXIII International Congress of Ophthalmology c/o Simul International Inc Kowa Bldg No 9 1-8-10 Akasaka Minato ku Tokyo 107 Japan.

The Third International Congress of Eye Research

will be held May 22 through 25 1978 at Nemuno Sato Japan

For further information contact Yoshizo Kikkawa M D Secretary Organizing Committee Department of Ophthalmology Osaka University Medical School 1 1 50 Fukushima Fukushima ku Osaka 553 Japan

The First International Symposium on Cataract Surgery

will be organized under the auspices of the Italian Ophthalmological Society directed by Prof G B Bietti and held in Florence at Palazzo dei Congressi April 15-17 1978

More than 50 eminent panelists of various nationalities will gather in order to focus the most modern surgical techniques and to discuss proper preventive and curative treatment either for complications or particular pathological and collateral situations

For information please contact Prof I Esente General Secretary Italian Ophthalmological Society C so Italia 2 50123 Florence Italy

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TRANSITORY BLINDNESS DURING ETHANOL AND PHENETHYLBIGUANIDE INDUCED LACTIC ACIDOSIS IN A SUBJECT WITH DIABETES MELLITUS

A Case Report

BY

PER NELLEMANN SORENSEN

Transitory blindness is described in a diabetic patient with typical ethanol and phenethylbiguanide induced lactic acidosis The blindness developed in the course of 8 hours but the vision returned during treatment with iv bicarbonate insulin and glucose
The condition is discussed in relation to a presumed inhibition of the oxidative metabolism in the retina

Key words diabetes – ethanol – lactic acidosis – phenethylbiguanide – phenformin – retinopathy – transitory blindness – oxidative metabolism

Several chemical agents and physical conditions can induce transitory or permanent loss of vision Well known are anoxia X ray irradiation high oxygen tension and administration of digitalis preparations quinine methylalcohol chloroquine iodate etc (Review Grymore 1970 Meier Ruge 1973 Potts 1967)

Since transitory blindness has not been reported in association with diabetes mellitus (Caird et al 1968 Leopold & Lieberman 1970) or lactic acidosis (Hermann 1973 Bengtsson 1972) the following case is described a patient

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with maturity onset diabetes and with ethanol and phenformin induced lactic acidosis presented with blindness on admission but the blindness improved during treatment with iv bicarbonate insulin and glucose

Case Report

The patient was a 5, year old obese woman with a diabetes of years duration. Because of poor regulation of diabetes and lack of acceptance of insulin injections phenethylbiguanide (= phenformin) was given 50 mg 2 times daily

During a short hospital stay for acute bronchitis a slight lactic acidosis was found. Standard bicarbonate was 19 9 meq/l (normal 21–25 meq/l) Arterial lactate and pyruvate 5 5 and 0 09 mmol/l (normal 0.55–1 ,5 mmol/l and 0 05–0 09 mmol l) The serum creatinine was normal 1 0 mg/100 ml In respect to blood glucose and urine ketone bodies the diabetes was well regulated

Ophthalmological examination Visual acuity 6 6 normal pupils and ophthalmoscopy

Eight month later i e 3 years after initiating phenformin therapy the patient was admitted to the hospital for amaurosis and dysregulation The patient had been drinking a considerable amount of alcohol the day before and on wakening was unable to discriminate between light and dark On admission she stated that she was blind

Visual acuity Light perception only The pupils were dilated and reacted extremely slowly to light Ophthalmoscopy was considered normal apart from peripheral narrowing of the arterioles

The clinical parameters were BP 120 60 mmHg (habitually 150 90) pulse 68 temp 36 5 C respiration normal no cyanosis arterial oxygen saturation 9 per cent slight anaemia 9 8 g 100 ml (normal 10 8–16 4 g/100 ml) ECG showed a remarkable ST depression in leads II and III which disappeared within one week Digitalis intake was denied Blood tests revealed a severe metabolic acidosis standard bicarbonate below 3.3 meq l (unmeasurable) serum chloride decreased to 86 meq/l (corresponding to an increase in organic anions) and blood lactate was 69 5 mmol/l (markedly elevated) Blood glucose was 150 mg 100 ml and no ketone bodies were found in the urine

Initially the condition was conceived as lactic acidosis (blood methanol was zero) and treatment was given with large doses of crystalline insulin 4 ml 40 IU ml over 8 hours glucose 200 ml 50 per cent over 4 hours and sodium bicarbonate 000 ml 5 per cent over hours In less than half an hour the vision recovered and the patient was able to read The pupils were the mediumsized and reacted better to light

Four hours after this vigorous treatment had begun, the patient had a period of clonic seizures BP fell to 100 50 mmHg and because of decreasing diuresis and slightly elevated serum creatinine the patient was transferred to a department of nephrology for haemodialysis Kidney biopsy a m Brun showed a diabetic angiopathy but no pathological changes consistent with acute tubulointerstitial nephropathy were seen (performed by Claus Brun M D) Blood ethanol was not performed

Ophthalmoscopy the next day showed narrowing of the arterioles especially in the

periphery and some arterio venous crossing phenomena The *optic disc was normal* as was the remainder of the fundus

Examination 2 years later showed diabetes simplex changes with microaneurysms small haemorrhages and small exudates The arterioles showed a uniform narrowing

Discussion

It is well known that phenethylbiguanide (phenformin) can induce lactic acidosis in diabetics (Bengtsson et al 1972) and it is known that alcohol intake pre disposes to this condition (Kreisberg et al 1972 Johnson & Waterhouse 1972) The condition is characterized by a severe primary acidosis with accumulation of organic anions especially lactate without any corresponding increase in pyruvate This acidosis has no relation to circulatory collapse (Huckabee 1961) severe anaemia liver damage or kidney disease (Tranquada et al 1966) In these cases the lactic acidosis is secondary and it recovers when the under lying disease is treated Many organs are involved in the essential form and confusion slight arterial hypotension and slight uraemia are found More than a hundred cases have been reported (Herman 1973 Vinik & Jackson 1974) but whereas a shift between normal and dilated pupils has been reported (Jensen & Hammer 1971) blindness has so far as we know not previously been described

This clinical situation with acidosis dilated and sluggishly reacting pupils decreased serum chloride a blindness which improves following bicarbonate treatment and ECG changes bears a strongly resemblance to methanol poisoning (Benton & Calhoun 1953 Grant 1974 Roe 1943) However blood methanol in our case was zero

The transitory blindness could not be explained by cerebral causes either Walsh (1969) only reports one case with acidosis His patient had a severe uraemia bue the blindness was related to the urea concentration

Other factors point to a decreased perfusion but the vision returned before the blood pressure was lowest However if the clinical situation is looked upon as an inhibition of the oxidative metabolism of the retina with a shift towards anaerobic metabolism the blindness seems to be explained Thus teleologically symptoms might be expected from the retina because of its unique high meta bolic rate with the ability to form lactic acid even under aerobic conditions (Graymore 1970)

An inhibition of oxidative metabolism could be mediated by a combination of the following factors I) the diabetic state II) the phenylethylbiguanide treatment III) the heavy ethanol consumption the evening before and IV) the slight anaemia

I) In the diabetic state there is a increased glycolysis and a increased lactate/pyruvate ratio both in the blood and intracellularly. In the retina the biochemistry has not been fully elucidated but evidence is presented for an increased glycolysis during alloxan diabetes in the rat (Graymore 19 0).

II) The precise action of phenethylbiguanide is not clear but the overall effect is reminiscent that gluconeogenesis is inhibited and the glycolysis enhanced (Haller & Strauzenberg 1966, Gordon 1973). A common site might be an interference with the oxidative phosphorylation (Creutzfeldt et al. 19 1, Gordon 1973), a hypothesis which is gaining increasing support from the *in vitro* and *in vivo* studies of inhibition of transport processes (Bloch et al 1973, Arvantinakis et al 1973, Sorensen 1977).

III) Ethanol acts by decreasing lactate utilisation in the liver and accentuates the phenethylbiguanide induced lactate production (Johnson & Waterhouse 1968, Kreisberg et al 1972).

IV) The slight anaemia might enhance the intracellular glycolysis through the Pasteur effect.

Normally in tissues there is more NAD than NADH. In lactic acidosis the ratio of the oxidised to reduced coenzyme is changed due to an increase in NADH. Such changes in the ratio of oxidised to reduced coenzymes may have complex effects on metabolism including that of the retina (Caird et al 1969).

An inhibition of the oxidative metabolism in the retina as a cause for the blindness in this patient is in harmony with the fact that many retinotoxic substances or conditions interfere with the supply of energy, e.g. anoxia, oubain, iodoacetate, azide (Graymore 1970). Sorsby (1955) tried to induce degeneration of the retina with such agents in sublethal doses but without impressive results. This was possibly due to the narrow gap which exists between death and retinal affection when such agents are used, as seen in the experimental methanol poisoning (Gilger & Potts 1955).

This phenomenon might account for the reason why the described transitory blindness has not been reported before.

Acknowledgment

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References

Arvantinakis C Lorenzsonn V & Olsen W A (19 3) Phenformin induced alterations of small intestinal function and mitochondrial structure in man *J Lab clin Med* 8? 195–?00

Bengtsson K Karlberg B & Lindgren S (19 2) Lactic acidosis in phenformin treated diabetics *Acta med scand 191* ?03–208

Benton C [illegible] Calhoun F & Phinizy F Jr (1953) The ocular effects of methyl alcohol poisoning Report of a catastrophe involving 3?0 persons *Amer J Ophthal 36* 16?7–1685

Bloch R Menge H Schaarschmidt W D Gottesburen H Schaumloffel E Goebell H & Riecken E O (19?3) Biochemische histochemische histologische und funktionelle Untersuchungen zur Phenforminwirkung auf die Dunndarmschleimhaut bei Ratte und Mensch *Klin Wschr 51* ?35–241

Caird F I Pirie A & Ramsell T C (1969) *Diabetes and the Eye* Blackwell Oxford

Creutzfeldt W Willms B & Caspary W F (19?1) *The mechanism of action of the blood glucose lowering biguanides* Reports on Oral Diabetes Therapy a Selection of Papers presented at the 7th Congress of the International Diabetes Federation Buenos Aires August 19?0 pp 95–106 Excerpta Medica Amsterdam

Gilger A P & Potts A M (1955) Studies on the visual toxity of methanol V The role of acidosis in experimentel poisoning *Amer J Ophthal 39* 63–86

Gordon E E (19 3) Etiology of lactic acidosis *Amer J med Sci* ?65 469–465

Grant M W (19?4) *Toxicology of the Eye* Charles C Thomas Springfield Illinois

Graymore C N (19?0) Biochemistry of the retina In Graymore C N [illegible] *Biochemistry of the eye* Academic Press London

Haller H & Strauzenberg S E (1966) *Orale Diabetes Therapie Biguanide* pp 2?3–4?2 VEB Georg Thieme Leipzig

Hermann L S (19?3) Biguanides and lactate metabolism a review *Danish med Bull* ?0 65–?9

Jensen H Æ & Hammer A (1971) Mælkesyreacidose hos diabetiker i fenformin behandling *Nord Med 85* 469–4?1

Johnson H K & Waterhouse C (1968) Relationship of alcohol and hyperlactatemia in diabetic subjects treated with phenformin *Amer J Med 45* 98–104

Leopold I H & Lieberman T W (19?0) The eye and diabetes mellitus In Ellenberg M and Rifkin H Eds *Diabetes Mellitus Theory and Practice* pp ?96–821 McGraw Hill New York

Meier Ruge W (19?3) Zur Ätiologie und Pathogenese toxischer Arzneimittelnebenwirkungen an der Netzhaut *Klin Mbl Augenheilk 163* 155–17?

Potts A M (1964) Selective action of chemical agents on individual retinal layers In Graymore [illegible] N Ed *Biochemistry of the Retina* pp 155–16? Academic Press London

Røe O (1946) Methanol Poisoning Its clinical course pathogenesis and treatment *Acta med scand 18? Suppl)*

Sorsby A & Nakajima A (1958) Experimental degeneration of the retina III Inhibitors of glycolysis and of respiration as inducing agents *Brit J Ophthal 4?* 558–56?

Sorensen P N (197) Phenformin induced inhibition of Hippuran accumulation in the ciliary body *In vivo* and *in vitro* studies To be published

Tranquada R F Grant W J & Peterson C R (1966) Lactic acidosis *Arch intern Med 117* 192–202
Vinik A I & Jackson W P U (1974) Lactic acidosis in Diabetics *Sth afr med J 48* 2021–2026
Walsh F B & Hoyt W F (1969) *Clinical neuro ophthalmology* 3rd ed Williams & Wilkins Baltimore

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MONOZYGOTIC TWINS WITH TEMPORAL ARTERITIS AND OPHTHALMIC ARTERITIS

BY

AXEL KEMP

Temporal arteritis – ophthalmic arteritis occurring in a pair of mono zygotic twins who were 7? and 77 years of age respectively at the onset of symptoms is reported It is pointed out that it is rare to see as in the first case an improvement in an already existing severely reduced vision in relation to corticosteroid treatment The importance of genetic factors in temporal arteritis is discussed further ■ is suggested that a possible association of the disease with tissue type antigens be the object of further study

Key words arteritis temporalis – arteritis cranialis – giant cell arteritis – heredity – corticosteroids – twins

Arteritis of the temporal arteries was described as a component of a new syndrome by Horton Magath & Brown (1934) Severe headache pronounced fatigue and an increased erythrocyte sedimentation rate are the most im portant symptoms of the disease Coexistence with rheumatic polymyalgia has been demonstrated where the symptoms are stiffness and pain in the neck and of the muscles of the proximal extremities (Alestig & Barr 1963) A con comitant ophthalmic arteritis is often seen in cases of temporal arteritis and this frequently affects both the posterior ciliary arteries and central retinal artery (Ry Andersen 1969) Ischaemic papillopathy with amaurosis or severe

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Walsh F B & Hoyt W F (1969) *Clinical neuro ophthalmology* 3rd ed Williams & Wilkins Baltimore

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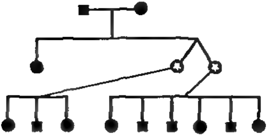

Fig 2
The family tree Squares males round dots females The affected twins are marked with a star

from severe fatigue and pains in both temporal regions she also had pains in the jaw and *throat following swallowing These symptoms had lasted for 3 months* during this period she twice suffered from blurred vision for approximately 30 min

Examination at the eye clinic did not reveal any abnormality visual acuity was 6 6 in both eyes The patient appeared slightly affected by the condition The temporal arteries could be palpated they were hard and no pulsation could be felt The heart action was regular and without any murmurs Blood pressure was 135 0

A biopsy from the right temporal artery showed temporal arteritis with typical changes (signed A Haug) *The patient suddenly developed a reduction in vision of the right eye* visual acuity = light perception Ophthalmoscopy of the right eye showed a flat pale prominence of the nerve head The vessels of the retina were unaffected She was immediately given 100 mg im of hydrocortisonum (Actocortin®) followed by 10 mg × 4 daily of prednisonum (Delcortin®) orally Following this her vision gradually improved over the following three days and after 12 days of this treatment *the visual acuity of the right eye was 6 24 and after one month it had further* improved to 6/12 (the left eye remained unaffected with a visual acuity of 6 6) The visual field of the right eye was initially decreased to a small temporal area but this was later enlarged to include the major portion of the normal temporal quadrants The general condition of the patient gradually improved and the drug treatment could be *discontinued after one year*

Laboratory tests on admission ESR = 56 mm/h rheuma tests blood count WR ECG and X ray of the thorax were normal Paper serum electrophoresis showed increased alpha 2 globulin and a reduced albumin (8 4 g/l and 32.3 g/l)

Case II

N II twin II The patient had lived in the same neighbourhood as her twin sister for *the whole of* her life Their common experiences had bound them together to an

extraordinary degree The patient was in the main healthy until the age of 71 years when she complained of increasing fatigue pains in the forehead temporal regions and neck together with a feeling of narrowness in the throat on swallowing and pains in the jaw on chewing As the symptoms increased in severity she administered to herself varying doses of the corticosteroid prescribed for her sister

The patients ESR was 8 mm/h when she consulted her doctor for the first time He referred her to an ophthalmologist who found her visual acuity in both eyes to be 6/9 ophthalmoscopy revealed slight macular retinal degeneration She suddenly developed total amaurosis of the left side following approximately 1½ h of metamorphopsia six weeks after the onset of the general symptoms On admission to the ophthalmological department her ESR was 38 mm/h the visual acuity of the right eye was 6/18 that of the left = no light perception Ophthalmoscopic examination of the right eye showed no changes the visual field was normal as tested by finger movements Severe ischaemic papillary oedema but normal retinal vessels were observed in the left eye There was no pulsation in the arterial system of the temporal regions and neck although no enlargement of the vessels could be felt The patient s general condition was fairly good The heart action was regular without any murmurs A systolic murmur of strength I could be heard above the right subclavian artery No murmurs could be heard above the arteries of the neck or cranium Her blood pressure was 160/90 and similar in both upper extremities

Biopsy from the frontal branch of the right temporal artery showed a thickened artery which did not bleed on cutting Histological examination showed a fairly fresh case of giant cell arteritis (signed S Ry Andersen) Treatment was started with an oral dose of 60 mg of prednisonum (Delcortin®) daily which was to be diminished under continued control of the ESR The pain and tiredness disappeared within 1 to 2 weeks but no improvement took place in the vision

Laboratory tests on admission Rheuma tests immuno globulins liver tests blood count WR ECG and X ray of the thorax were normal Se haptoglobin Se orosomucoid and Se alpha 1 antitrypsin were increased (3 1 g/l 1 3 g/l and 3 59 g/l) The Se albumin was reduced (31 g/l)

Zygosity diagnosis

As children both J J and N B were often mistaken for one another owing to their mutual likeness In 1976 J J was 148 cm high while N B was 140 cm An extensive investigation of blood serum and enzyme groups revealed complete identity between the partners The diagnosis of monozygosity was hereby established (Hauge 1962)

The full results of the examination of 16 systems were O MS+s– C+Cw–D+E–c+ P+ K– Fy(a–) PGM 1–1 SP B AK 2–1 PGD A ADA 1–1 GPT 1–1 Hp 2–2 Gc 1–1 Gm (a–x–b+) HLA A9 w26 B12 27 Cw3 w5

Clinical comments

Treatment with corticosteroids has for some considerable time been the accepted form of treatment for temporal arteritis because of its prophylactic effect The drug stops progression of the disease in the ophthalmic area (Birkhead et al 1957) The case history of J J demonstrates the rare occurrence (Boghen & Glaser 1973) of a pronounced improvement in the severely reduced visual acuity which follows ischaemic papillopathy (see however Neu 1959 Simmons & Cogan 1962 Norn 1966 Cullen 1967 Hamrin 1972 Johnston 1973 Eagling et al 1974) On the other hand the case history of N B shows as earlier emphasized by Svane Knudsen (1960) that a (presumably) rather low dosage of corticosteroid does not give sufficient prophylactic effect during the eruptive stage to stop progression of the disease The self administration of the drug by the patient probably masked the cardinal symptom which a very high erythrocyte sedimentation rate is considered to be prior to the ocular crisis (Palm 1958)

General Discussion

It is difficult to trace cases of temporal arteritis in the same family as the disease on the whole develops late (approximately 70 years of age (Norn 1966)) In addition the incidence is presumably fairly low Many patient series have been published since 1934 including larger series compiled from previously published reports (for a survey see Hamrin 1972) Further patient series have been published of ischaemic optic neuropathy (for example Cullen 1967 Boghen & Glaser 1973 Eagling et al 1974) In these temporal arteritis is considered one of the major pathogenetic factors

Bang (1964) estimated the incidence of the disease by carrying out a survey of the reports from the medical departments of Danish hospitals Thus for 1959 he found 19 cases among 182 185 hospitalized patients I have carried out a more limited survey (using the annual hospital reports) of a number of medical departments in the period 1970 to 1975 and found 24 cases among only 29 724 admissions The higher incidence was expected and presumably reflects the improved diagnosis In the Danish ophthalmological departments temporal arteritis was diagnosed in 11 and 15 cases for the years 1973–74 and 1974–75 respectively (information from the departments)

A recent scrutiny of the Danish Twin Register which comprises nearly all Danish twins born between 1880–1910 (Hauge et al 1968) revealed no veri

fied case of temporal arteritis among 4374 same sexed pairs for whom a complete medical history including information on all hospital admissions was available (Hauge 1976)

The fact that the finding of the pair of twins as described in the present study is unique both weakens and strengthens the importance of the finding Thus it is necessary to carry on accumulating data of the same type The *possibility of exogenic factors which could have produced or contributed to* the development of the disease has been studied further by means of sup plementary interviews with the two patients However these gave no results The five year difference in the onset of the disease would not specifically suggest the predominance of exogenic factors Vogt (1935 1938) has on the other hand in 34 pairs of monozygotic twins between the ages of 55 and 81 years shown that aging occurs simultaneously in both twins i e the changes in hair face and eyes including those of the central fundus He also reported the occurrence of dramatic changes of the eye Acute haemorrhagic retinitis developed in one eye together with less pronounced changes in the other in two female twins at the age of 80 years Vogt concludes that all the phenomena *as described by him have no relation to environment and that* they are governed entirely by both genomes

The aetiology of temporal arteritis or giant cell arteritis is unknown Rahi & Garner (1976) consider it most reasonable to suspect an autoallergic process triggered by damage to the smooth muscle cells of the arteries In their de scription of autoimmune disease concepts they state that autoimmune responses may include a genetic component Richardson (1963) also classified the syn drome as a connective tissue disorder but he states that there is only little evidence to suggest a genetic basis for these (see also Peterson & Good 1963)

A possible genetic mechanism could involve an association with tissue type antigens in the same manner as has already been demonstrated with con siderable significance for a number of diseases (*McDevitt & Bodmer 1974*) It may therefore be profitable to tissue type a number of patients suffering from temporal arteritis

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References

Alestig K ■ Barr J (1963) Giant cell arteritis A biopsy study of polymyalgia rheumatica *Lancet 1* 1228–1230

Andersen ■ Ry (1969) Giant cell arteritis Horton Magath Brown temporal arteritis cranial arteritis *Trans Pacific Coast Oto Ophthal Soc* 35–58

Bang J (1964) Arteritis temporalis (in Danish) *Ugeskr Læg 126* 1513–1516

Birkhead N C Wagener H P & Schick R M (195) Treatment of temporal arteritis with adrenal corticoids *J Amer med Ass 163* 821–827

Boghen D R & Glaser J (1973) Ischaemic optic neuropathy Clinical features and long term follow up *Trans Amer neurol Ass 98* 256–258

Cullen J F (1967) Ischaemic optic neuropathy *Trans ophthal Soc U K 87* 759–7 4

Eagling E M Sanders M D & Miller S J H (1974) Ischaemic papillopathy Clinical and fluorescein angiographic review of forty cases *Brit J Ophthal 58* 990–1008

Hamrin B (1972) Polymyalgia arteritica *Acta med scand Suppl 533* 1–131

Hauge M (1969) Om blodtypernes anvendelse i den humane genetik (in Danish English summary) *Ex Domo Biol Hered Hum Un Hafn* 102–119 & 197

Hauge M Harvald B Fisher M Gotlieb Jensen K Juel Nielsen N Raebild I Shapiro R & Videbech T (1968) The Danish twin register *Acta Gen Med Gemellol 17* 315–332

Hauge M (1976) Unpublished data

Hayreh S S (1970) Pathogenesis of visual field defects Role of the ciliary circulation. *Brit J Ophthal 54* 289–311

Horton B T, Magath T B & Brown G E (1934) Arteritis of the temporal vessels A previously undescribed form *Arch intern Med 53* 400–409

Johnston A C (1973) Giant cell arteritis Ophthalmic and systemic considerations *Canad J Ophthal 9* 39–46

McDevitt H & Bodmer W F (1974) HL A immune response genes and disease *Lancet 1* 1269–1275

Neu H J (1959) Gunstiger Verlauf einer doppelseitigen Erblindung bei Arteritis temporalis *Klin Mbl Augenheilk 134* 250–259

Norn M S (1966) Arteritis temporalis 13 tilfælde fra en kobenhavnsk øjenafdeling (in Danish) *Ugeskr Læg 128* 53 –537

Palm E (1958) The ocular crisis of the temporal arteritis syndrome (Horton) *Acta ophthal (Kbh) 36* 208–243

Peterson R D A & Good R A (1963) Interrelationships of the mesenchymal diseases with consideration of possible genetic mechanisms *Ann Rev Med 14* 1–40

Rahi A H S & Garner A (1976) *Immunopathology of the eye* 60–74 & 303–305 Blackwell Oxford

Richardson J (1963) *Connective tissue disorders* 1–239 Blackwell Oxford.

Simmons R J & Cogan D G (1962) Occult temporal arteritis *Arch Ophthal (Chicago) 68* 8–18

Svane Knudsen P (1960) Bilateral ophthalmic arteritis as part of the temporal arteritis syndrome *Acta ophthal (Kbh) 38* 408– 12

Vogt A (1935) Die senile Determination des Keimplasmas beobachtet an eineiigen Zwillingen des 55 bis [illegible] Jahres *Schweiz med Wschr 65* 576–579
Vogt A (1938) Weitere Augenstudien an eineiigen Zwillingen hoheren Alters uber die Vererbung der Altersmerkmale *Klin Mbl Augenheilk 100* 496–544

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OPTIC DISC DRUSEN AND TUMOURS OF THE CHIASMAL REGION

BY

EILA MUSTONEN

Two patients with optic disc drusen and tumour of the chiasmal region are presented The association of optic disc drusen and intracranial space occupying lesion is probably a chance occurrence In spite of the recognition of the optic disc drusen certain findings indicate further examinations Progressive loss of central visual acuity unexplained by retinal pathology is an indication for a neurological investigation. Bi temporal and homonymous hemianopic visual field defects as well as evidence of papilloedema warrant a neurological evaluation

Key words drusen – hyaline bodies – optic chiasm – optic disc – perimetry – pituitary tumour

The first report of optic disc drusen was a histological study by Muller (1858) Liebreich (1868) gave the first description of the ophthalmoscopical appearance of drusen Optic disc drusen are anomalous hyaline bodies of the optic nerve heads situated in front of the lamina cribrosa They are laminated homogeneous masses which frequently become calcified The occurrence of drusen in the general population is 3 4 per thousand according to Lorentzen (1966)

Optic disc drusen can be 1) idiopathic nonfamilial sporadic cases or familial showing an irregularly dominant autosomal transmission or they can be 2) associated with other pathology such as optic atrophy vascular anomalies retinitis pigmentosa tuberous sclerosis or angioid streaks

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Optic disc drusen are bilateral in 75 % of cases They can be superficial visible refractile yellowish white nodules on the optic discs or embedded deep in the tissue of the discs These buried drusen of the optic discs are the main cause of difficulty in the diagnosis of early papilloedema

Optic discs with drusen show no hyperaemia no exudates and usually no venous congestion The disc margins are irregular and blurred and a nodular edge can easily be seen with oblique transillumination The physiological cup is filled in Vascular anomalies in the form of arterial or venous loops may be found in 11 % of cases (Lorentzen 1966) Spontaneous venous pulses may be absent

Visual field defects occur in 85 % of cases – by compression causing atrophy of the adjacent nerve fibres or on a vascular ischaemic basis Central visual acuity usually remains normal although about 50 % of cases show a slow progression of visual field defects Visual fields may reveal enlargement of the blind spots nerve fibre bundle arcuate scotomas nasal sector or quadrant defects or peculiar irregular concentric contractions

In fluorescein angiography control photographs taken prior to fluorescein injection with filters in place show bright images with superficial drusen of the disc This is perhaps partially reflected light and partially true autofluorescence (Kelley 1974) Normal optic discs are black in these pictures The drusen show a fluorescence that may slightly increase during the study but does not extend into the surrounding retina or along the retinal vessels No leakage is found The drusen show irregular nodular density of fluorescence

Haemorrhages can occur with optic disc drusen Progressive enlargement of the drusen may gradually lead to back pressure and stasis in the retinal veins or mechanical erosion of the adjacent vessel may occur as a result of progressive enlargement of the hard calcified drusen Haemorrhages may be small splinter like in the substance of the disc usually not producing symptoms Sometimes they may rupture into the vitreous body producing visual disturbance Deep subretinal peripapillary haemorrhages cause visual disturbance and permanent visual field defects and can cause confusion with a choroidal melanoma

Intracranial space occupying lesions are not common in the presence of optic disc drusen The recognition of optic disc drusen makes intracranial tumour an unlikely diagnosis but does not preclude it The association of these two conditions is probably a chance occurrence But progressive loss of central visual acuity unexplained by retinal pathology is an indication for a neurological evaluation Bitemporal and homonymous hemianopic field defects warrant a neurological investigation

Previous reports of optic disc drusen and intracranial space occupying lesions are presented

Kath (1888) – a pituitary tumour
Feijer (1909) – a tumour at the base of the brain
Lauber (1913 1921) – a pituitary tumour
François (1949) – a cerebral abscess in the temporal region
Chambers & Walsh (1951) – an intracranial tumour
Kurus (1955) – a craniopharyngioma
Harms (1960) – a meningioma of the tuberculum sellae
Rucker & Kearns (1961) – a meningioma behind the right optic nerve
Stiefel & Smith (1961) – a chromophobe pituitary adenoma
(Okun (1962) – multiple meningiomas)
Lorentzen (1966) – a suspected suprasellar tumour
Ben Zur & Lieberman (1972) – a meningioma en plaque

Most of these intracranial space occupying lesions were tumours of the chiasmal region

Two cases are presented with optic disc drusen and tumour of the chiasmal region.

Case Reports

Case 1 R N

The first patient is a 38 year old man whose family history and previous history were unremarkable In 1971 he went to see a private ophthalmologist because of

Fig 1
Case 1 Fundus photographs of the right and left optic disc showing superficial drusen

Fig 2
Case 1 Autofluorescence of optic disc drusen in the control photographs of the right and left optic disc taken prior to fluorescein injection with filters in place

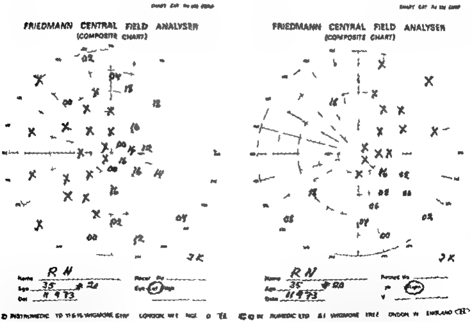

Fig 3
Case 1 Friedmann central visual fields showed bitemporal defects in September 1973

visual blurring for about four months headaches during his morning shift of work and depression for several years Visual acuity in both eyes was 0 8 Harrington Flocks multiple pattern fields showed no clear defects but there was some uncertainty in the upper field of the right eye and in the temporal field of the left eye He was referred to Oulu University Hospital because of these findings and of the odd looking optic discs with blurred margins

His visual acuity in the right eye was with correction 0 7 and in the left eye 0 9 Visual fields showed some defects and they were suggested to be caused by drusen of both optic discs (Fig 1) The patient was told that his optic nerve heads were anomalous and that this was not connected with his headaches but could explain the *slight blurring of vision* The patient was reassured and he was later treated by a psychiatrist because of depression and headaches

I saw the patient for the first time when he returned to Oulu University Hospital two years later in September 1973 because he felt that his vision had deteriorated and he experienced difficulties with side vision He could no longer read without difficulty the different gauges and gas meters at his work Headache had been worse for some months

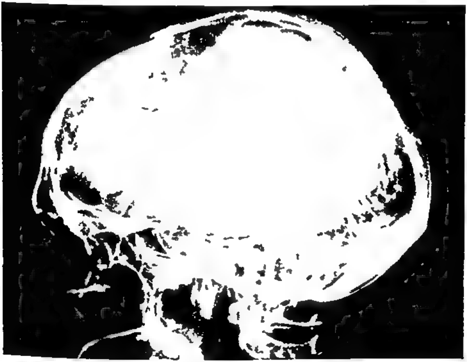

Fig 4

Case 1 Skull X rays revealed enlarged sella with destruction

13

Fig 5
Case 1 PEG revealed a large tumour pushing the third ventricle upwards

The visual acuity in both eyes with slight myopic correction was 1 0 As before optic discs showed drusen as we see in the control photographs taken prior to fluorescein injection (Fig 2) Visual fields revealed bitemporal defects (Fig 3) The patient was referred to the Neurology Department Neurological examination was normal Skull X rays revealed enlarged sella with destruction (Fig 4) EEG was normal Spinal fluid protein was moderately elevated (90 mg/100 ml) PEG revealed a large tumour pushing the third ventricle upwards and the suprasellar cisterns up and sidewards (Fig 5) A left carotid angiogram showed the same large sellar tumour displacing the anterior cerebral arteries No abnormal circulation was found and there was no tumour staining A chromophobe adenoma was suspected Laboratory tests with hormone studies were normal

Frontal craniotomy was done an adenoma was evacuated and its prechiasmal capsule removed Histology revealed a chromophobe adenoma Shortly after operation the right visual acuity was 0 5 and the left 0 15 The patient was referred to an endocrinological work up and since then has had substitution therapy Radiotherapy was given in March and April 19 4 five months after operation After radiotherapy a neuro ophthalmological examination showed bitemporal visual field defects but visual acuity with correction in the right eye was 1 0 and in the left eye 1 1 Temporary variable double vision was explained by exophoria and insufficient fusion or by bitemporal field defects No extraocular muscle palsy was found

Since then he has been examined at regular intervals A year ago visual fields showed bitemporal defects and a recent examination did not reveal any progression of the defects Fields were perhaps slightly better than before

Case 2 M K

The second patient is a 29 year old woman with a family history of obesity Previous history revealed latent diabetes during pregnancy in 19 3 After delivery her weight increased by 9 kg She had some polydipsia for one year In March 19/4 she had visual blurring for a few days

In June 19/4 she came to Oulu University Hospital for eye examination complaining of visual blurring in both eyes for two weeks and a slow decrease of central vision She could only read the largest newspaper print She had no pains on eye movements no headache and no other complaints

Her visual acuity in both eyes was counting fingers at three metres Optic discs were slightly elevated the physiological cup was filled in veins were normal but spontaneous venous pulses were absent No hyperaemia of the discs was found (Fig 6) Oblique transillumination revealed a refractile crystal in the tissue of the left optic disc The right macula was normal the left macula showed pigmentary changes Visual fields revealed large central defects These defects were variable and at first even a hysterical functional amblyopia was suspected

I saw the patient on June 1° 19/4 when her visual acuity was 0 1 in both eyes Because of visual field defects (Fig 7) a chiasmal lesion was suggested and a neurological and neuroradiological examination was recommended Laboratory tests including hormone studies were normal Spinal fluid was normal Skull X rays showed an anomalous intermediate clinoid process Farnsworth 15 colour test revealed red green disturbance A fluorescein angiogram showed optic disc drusen (Fig 8) and left macular pigment epithelium window defects No corticosteroids were given Fluctuating visual field defects made me think of a possible craniopharyngioma

Neurological examination was normal EEG was normal Brain scan was normal but PEG showed a large round suprasellar tumour displacing the interpeduncular

Fig 6

Case 2 Fundus photographs of the right and left optic disc showing slightly elevated and blurred margins Oblique transillumination revealed a refractile crystal shown with an arrow

visual field defects were thought to be caused by drusen Later bitemporal field defects warranted a neurological examination The second patient had such grave visual symptoms that an intracranial space occupying lesion was suspected and optic disc drusen were merely an unessential finding PFG could be performed without any great risk because drusen revealed that the elevation and fullness of the discs were not caused by papilloedema Auto fluorescence of drusen was helpful in this case

References

Ben Zur P H & Lieberman T W (1972) *Drusen of the optic nerves and menin gioma A case report Mt Sinai J Med 39/9* 188–196

Chambers J W & Walsh F B (1951) Hyaline bodies in the optic discs Report of ten cases exemplifying importance in neurological diagnosis *Brain 74* 95–108

Fejer J (1909) Über die Drusen des Sehnervenkopfes *Graefes Arch Ophthal 7* 454–455

François P (1949) Les *verrucosites hyalines de la papille Ann Oculist (Paris) 18* 249–278

Harms H (1960) Fall von Drusenpapillen *Klin Mbl Augenheilk 136* 127

Kelley J S (1974) Autofluorescence of drusen of the optic nerve head *Arch Ophthal (Chicago) 92* 263–264

Kurus [redacted] (1955) *Zur Definition der Drusenpapille Ber dtsch ophthal Ges 59* 46–47

Lauber H (1913) Drusen des Sehnerven *Z Augenheilk 19* 201

Lauber H (1921) Klinische und anatomische Untersuchungen uber Drusen im Seh nervenkopf *Graefes Arch Ophthal 105* 567–589

Liebreich R (1868) Contribution to discussion on Iwanoff A Ueber Neuritis optica *Klin Mbl Augenheilk 6* 426–427

Lorentzen S E (1966) Drusen of the optic disk A clinical and genetic study *Acta ophthal (Kbh) Suppl 90* 1–180

Muller H (1858) Anatomische Beitrage zur Ophthalmologie *Graefes Arch Ophthal 4* 1–40

Okun [redacted] (1962) Chronic papilledema simulating hyaline bodies of the optic disc *A case report Amer J Ophthal 53* 922–927

Rath W (1888) Beitrag zur Symptomenlehre der Geschwulst der Hypophysis cerebri *Graefes Arch Ophthal 34* 81–130

Rucker C W & Kearns T P (1961) Mistaken diagnoses in some cases of menin gioma *Amer J Ophthal 51* 15–19

Stiefel J W & Smith J L (1961) *Hyaline bodies (drusen) of the optic nerve* and intracranial tumor *Arch Ophthal (Chicago) 65* 814–816

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THE ULTRASTRUCTURE OF LENS AND IRIS IN CEREBROTENDINOUS XANTHOMATOSIS

BY

JOHAN H SELAND and JON E SLAGSVOLD

The lens and an iris biopsy from a patient with cerebrotendinous xanthomatosis has been examined in the electron microscope Subepithelial electron lucent areas were demonstrated The iris was normal The lens changes were thought to be due to deposition of the specific cholesterol breakdown product inherent to this disease

Key words cerebrotendinous xanthomatosis – lens – iris – electron microscopy

Cerebrotendinous xanthomatosis (CTX) is a rare familial autosomal disease which seems to be inherited as a Mendelian recessive It was first described by van Bogaert et al in 1937 and only about 30 cases have been reported in the literature (van Bogaert et al 1937 Menkes et al 1968 Harlan & Still 1968 Salen 1971 Schreiner et al 1975)

CTX is characterized by tendon xanthomas and bilateral juvenile cataracts followed by progressive dementia and cerebellar ataxia The first specific manifestations of the illness appear in late childhood or early adolescence At that time patients develop bilateral zonular or radial cataracts palpebral xanthelasmas and enlargement of Achilles tendons The condition progresses slowly Death usually occurs during the sixth or seventh decade and is often due to unrelated causes Terminally visual loss with palor of the optic discs have been reported (Menkes 1970)

The disease is due to a defect in cholestanol metabolism (Menkes et al

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1968 Philippart & van Bogaert 1969) This sterol 5α cholestan 3β ol is thought to be a catabolic degradation product of cholesterol (Salen & Polito 1972) Normally small amounts are present in most human tissues (Menkes 1970 Salen 1971) In CTX different investigators have found abnormally high concentrations of cholestanol deposited within the nervous system (Menkes et al 1968) the tendons (Philippart & van Bogaert 1969) and other tissues (Salen 1971) including the rectus muscles of the eye This generalized distribution has led to the designation Cholestanolosis (Philippart & van Bogaert 1969) The basic biochemical defect has not as yet been identified but some reports in recent years suggest abnormalities in hepatic sterol synthesis and bile acid metabolism (Salen & Grundy 1973 Setoguchi et al 1974)

The diagnosis of CTX should be suspected if cataract and achilles tendon xanthomatosis are observed in a patient before the age of 30 years (Farpour & Mahloudji 1975) The definite diagnosis is established by the measurement of elevated plasma or tissue cholestanol concentrations (Salen 1971)

Cataract in CTX is poorly documented in the ophthalmological literature The cataractous changes usually appear in the anterior cortex later followed by changes in the posterior parts of the lens Vindotti (1950) suggested that transient serum cholesterol elevations were associated with an exacerbation of cataract The hypothesis that lens opacities might be due to lipid deposition was put forward by Schimschock (1968) These early studies had however no access to chemical analysis concerning cholestanol deposits in tissues Kearns & Wood (1976) reported a case involving a young man with one aphakic eye the other eye showing evidence of lens changes with deterioration of vision An extracapsular cataract extraction was undertaken We are only aware of one report concerning lipid analysis and microscopy of the lens (Harlan et al 1968) These authors originally published their case as a new entity but Salen (1971) has later proved it to be a true case of CTX Light and electron microscopy of the lens revealed no specific abnormalities The patient had a mild familiar diabetes and the lens changes were consistent with a diabetic cataract

We have studied the lens and iris from a patient with CTX by means of electron microscopy The diagnosis was established by classical biochemical and histological changes This case has been published from the medical point of view by Schreiner et al (1975)

Case Report

A housewife born in 1935 was first seen in 1972 complaining of gradually deteriorating vision starting four years previously Her parents were first cousins alive and well without signs of CTX Her mother had a senile cataract successfully ex

tracted at the age of 50 years. The achilles tendons of the patient had been thickened from the time of mid adolescence. After her second pregnancy she experienced an increase in body weight. She later developed dyspnoea, ataxia and vertigo.

Ophthalmological examination in 1972 revealed no palpebral xanthelasma and she had normal anterior segments. The lenses of both eyes showed evidence of nuclear and cortical changes, the left eye being more affected than the right. The opacities were located subcapsularly, both anteriorly and posteriorly. They appeared as irregular white dots which in some parts mimicked whirls. Nuclear changes were diffuse, the red reflexes were especially reduced centrally. Visual acuity of the right eye 6/18 −6.0 sph, the left eye 6/60 −10.0 sph. Visual fields and intraocular pressures were normal.

In 1975 she was admitted to hospital for a cataract extraction of the left eye as her vision had deteriorated. Due to the age of the patient chymotrypsin was used for 3 min after a basal iridectomy had been performed. The lens was extracted intracapsularly with a cryopencil. There were no complications during or following the operation. Postoperatively the fundus could be examined and we found a normal optic disc and retina. The final visual acuity was 6/9 +13.0 sph. The cataractous right lens was removed 4 months later using an identical extraction method. The final visual acuity of this eye was 6/9 +12.0 sph ⊃ −1.0 cyl 0°.

Material and Methods

The extracted left lens and iris tissue were fixed in 3 % phosphate buffered glutaraldehyde for 72 hours. A slice of the lens was cut through its axis and the cross section was subdivided into thirteen subsections (see Fig. 1). All lens sections and the iris tissue were postfixed in osmium tetroxide and dehydrated through increasing concentrations of alcohol and finally through propylenoxide to Epon 812. After polymerisation, ultrathin sections were cut on a LKB

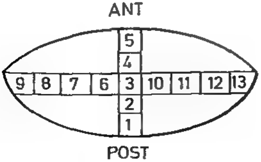

Fig. 1

Diagram showing subdivisions of the lens areas examined in the electron microscope

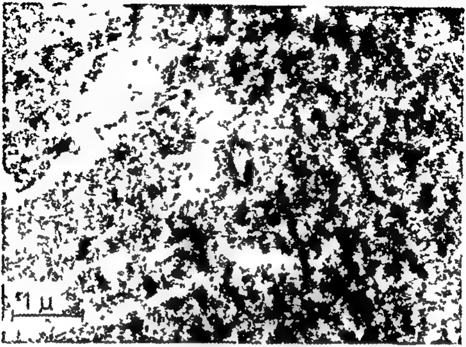

Fig 2

Area 4 (see Fig 1) Note the linear cleft like area and the more confluent areas with low electron density surrounded by mottled lens fibre substance × 16 400

ultramicrotome and stained with lead and uranyl and examined in a Philips EM 300 electronmicroscope

The right lens was immediately deep frozen and sent to gaschromatographic analysis to determine the content of cholestanol and cholesterol

Results

The posterior and nuclear sections of the lens (1 2 3 6 and 10) showed no gross abnormalities apart from mottling of the granular structure of the lens fibers In the anterior cortex (4) distinct abnormalities were found Clefts and confluent areas of low electron density could be observed (Fig 2) Similar changes were also very pronounced in area 8 and 12 Many of the cells especially in the anterior polar region had numerous vacuoles which were partially disrupted and filled with dispersed granular content (Fig 3) Cells in the equatorial region appeared normal The sections from the iris showed no pathological changes (Fig 4)

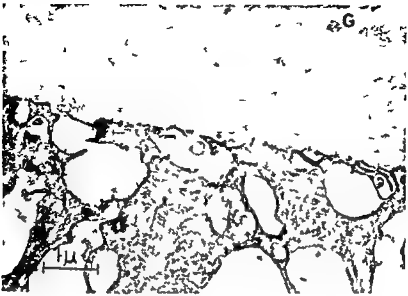

Fig 3
Area 5 (see Fig 1) Numerous vacuoles in the epithelial cells The capsule seems normal G granular lens capsule inclusion × 13 600

By gaschromatographic analysis of the right lens significantly elevated amounts of cholestanol were found This amount was however appreciably lower than the cholesterol content Normal cataract lenses were used as controls

Discussion

Earlier reports have dealt with the histological and ultramicroscopical appearances of the extra ocular tissues in this condition From these reports the most pronounced pathological features seem to be

1 Fans of needle like clefts which are assumed to be filled with cholestanol *in vivo*

2 Foam cells containing lipid

No specific ultramicroscopic lens changes have previously been demonstrated in this disease although early cataract localized posteriorly and anteriorly in a zonular configuration is a prominent feature of the condition

Care has been taken to avoid artifacts and the electronlucent clefts and areas in the anterior cortical regions seem to be genuine pathological changes

Fig 4
Section from iris Normal melanocyte (M) containing dark pigment granules N transected nerve fibres F Muscle fibres x 16 400

One might suggest that they are caused by an accumulation of degradation products specific to this disease but the exact nature of these accumulates has not been determined The other lens from this patient was however found to contain raised amounts of cholestanol and cholesterol

The vacuoles found in the epithelial cells at the anterior polar region might be an α chymo trypsin effect The disease does not seem to manifest itself in iris tissue

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References

van Bogaert L Scherer H J & Epstein E (1937) *Une forme cérébrale de cholestérinose généralisée* Masson et Cie Paris

Farpour H & Mahloudji M (1975) Familiar Cerebrotendinous Xanthomatosis Report of a New Family and Review of Literature *Arch Neurol (Chic) 32* 223–225

Harlan W R Jr & Still W J S (1968) Hereditary Tendinous and Tuberous Xanthomatosis without Hyperlipemia *New Engl J Med 278* 416–422

Kearns W & Wood W S (1976) Cerebrotendinous Xanthomatosis *Arch Ophthal (Chicago) 94* 148–150

Menkes J Schimschock J R & Swanson P D (1968) Cerebrotendinous Xanthomatosis The Storage of Cholestanol within the Nervous System *Arch Neurol (Chic) 19* 47–53

Menkes J (1970) Cerebrotendinous Xanthomatosis Vinken Bruyn *Handbook of Clinical Neurology Vol 10* 532–541 North Holl Publ Comp Amsterdam

Philippart M & van Bogaert L (1969) Cholestanolosis (Cerebrotendinous Xanthomatosis A Follow up Study on the Original Family *Arch Neurol (Chic) 21* 603–610

Salen G (1971) Cholestanol Deposition in Cerebrotendinous Xanthomatosis A possible Mechanism *Ann intern Med 75* 843–851

Salen G & Polito A (1972) Biosynthesis of 5alpha cholestan 3beta ol in Cerebrotendinous Xanthomatosis *J clin Invest 51* 134–140

Salen G & Grundy Scott M (1973) The Metabolism of Cholestanol Cholesterol and Bile Acids in Cerebrotendinous Xanthomatosis *J clin Invest 52* 2822–2835

Schimschock J R Alvord E C Jr & Swanson P D (1968) Cerebrotendinous Xanthomatosis Clinical and Pathological Studies *Arch Neurol (Chic) 18* 688–698

Schreiner A Hopen G & Skrede S (1975) Cerebrotendinous Xanthomatosis (Cholestanolosis) Investigations on Two Sisters and Their Family *Acta neurol Scand 51* 405–416

Setoguchi T G Salen G Tint G S & Mosbach E H (1974) A Biochemical Abnormality in Cerebrotendinous Xanthomatosis *J clin Invest 53* 1393–1401

Truswell A S & Pfister Peter J N S (1972) Cerebrotendinous Xanthomatosis *Brit med J 5* Febr 353–354

Vindotti D (1950) Una rare lipoidosi di interesse ortopedico Forma cerebrotendinea della cholesterinosi generalizzata *Chir Organi Mov 34* 429–438

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ATROPHY OF OPTIC NERVE FIBRES IN COMPRESSION OF THE CHIASM

Prognostic Implications

BY

MATS LUNDSTRÖM and LARS FRISÉN

A relationship between the degree of atrophy of retinal nerve fibres and visual field defect has been described in postoperative steady state patients (Lundstrom & Frisen 1976) The same factors were studied prior to surgery in six patients with compression of the chiasm due to chromophobe adenoma In five *eyes* the field defect was excessive in relation to the degree of atrophy After surgery the visual field defects improved to a level corresponding to the degree of atrophy in these eyes
In the remaining seven eyes there was a close correspondence between the atrophy and the visual field defect already before surgery The visual field defects remained unchanged in these eyes Provided that atrophy does not increase after surgery simultaneous preoperative evaluation of retinal nerve fibre atrophy and visual field defect allows an accurate prediction of prognosis for improvement

Key words optic atrophy – *optic chiasm* – pituitary tumour – visual field – ophthalmoscopy

Chiasmal lesions due to pituitary adenomata are rarely completely reversible The vast majority of patients present objective signs in the retinal nerve fibre layer of irreversible loss of visual pathway axons In postoperative steady state patients these fundus changes correspond closely to the degree and distribution of visual handicap (Lundstrom & Frisen 1976) Such a relationship does not apply in most patients with untreated lesions prior to surgery visual

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impairment is often more pronounced than could be expected from the amount of axonal wasting The discrepancy between the level of function and the extent of anatomical damage can be used to predict the maximum degree of visual improvement that can be expected following surgery as will be shown in this report Our observations are based on six patients with chiasmal lesions due to chromophobe adenoma studied prior to and following surgery

Material and Methods

Six patients with chromophobe adenoma were examined before and after un complicated transcranial surgery Age and follow up periods are shown in Table I

In every case the peripapillary retinal nerve fibre layer and the optic disc were studied with the funduscopic and photographic techniques described in a previous paper (Lundstrom & Frisen 1976)

A simple system was used for regional grading of atrophy of the retinal nerve fibre layer and the optic disc The state of the nerve fibre layer was evaluated in four peripapillary sectors temporal (papillomacular fibres) nasal above and below The optic disc was evaluated separately

Normal appearance was given a score of 0 partial atrophy a score of 1 and total atrophy a score of 2 Scores were summed for each eye separately A normal nerve fibre layer and a normal disc score 0+0+0+0+0 = 0 a complete

Table I
Patients with chiasmal compression due to chromophobe adenoma
Age and postoperative follow up periods

Case	Age (years)	Follow up period (months)
1	30	6
2	33	6
3	46	9
4	70	8
5	46	12
6	42	3

Fig 2 A B C

A Case 1 left eye Note lack of visible nerve fibres in the horizontal peripapillary sectors B Preoperative visual field examinations Score 2 C Postoperative visual field examination Score 2

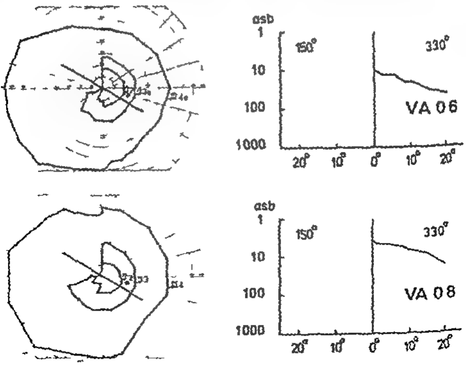
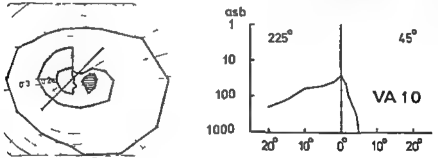
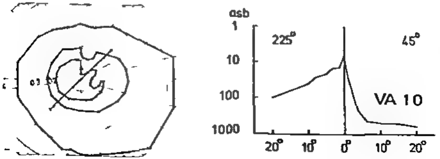


Fig 3 A B C

A Case 2 right eye Consult the text for details B Preoperative visual field examinations Score 2 C. Postoperative visual field examinations Score 1





sharp disc borders The atrophy score was 2+2+0+0+1 = 5 (Fig 2 A) The field and atrophy scores place this eye in the steady state area of Fig 1 and our prediction was that no or only a small improvement of the visual field was possible

Six months after surgery there were still relative temporal field defects in both quadrants scoring 2 (Fig 2 C) Visual acuity was 0 8 (-0 5 sph) The atrophy score was unchanged The prediction was correct.

2 Secretary aged 33 years with a six year history of amenorrhoea An air study showed a slightly dilated 3rd ventricle and a 2 cm large suprasellar mass At craniotomy the pituitary tumour was noted to displace the optic chiasm and the left optic nerve

Before surgery visual acuity of her right eye was 1 0 (± 0) There were relative temporal defects in both quadrants score 2 (Fig 3 B) The atrophy score was 2 (Fig 3 A) Based on these observations recovery of the visual field defect to score 1 was predicted

Six months following surgery a relative upper temporal defect remained score 1 (Fig 3 C) Visual acuity was unchanged as was the atrophy score The prediction was correct

3 Nurse aged 46 years with a six month history of headache Accentuated difficulties in reading during the last few weeks An air study showed a suprasellar mass

Before surgery visual acuity of her *right* eye was 0 8 (+2 0 sph) There were relative field defects in both temporal quadrants score 2 (Fig 4 B) Ophthalmoscopy showed a prominent nerve fibre layer and the optic disc seemed normal score 0 (Fig 4 A) Full recovery was predicted

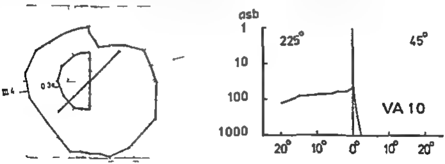
Nine months following surgery visual acuity was 1 0 (+2 0 sph) There was neither a demonstrable visual field defect nor any sign of atrophy Our prediction was correct

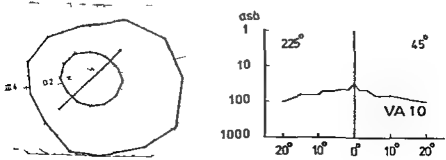
In her *left* eye the visual acuity was finger counting before surgery There were absolute field defects in two quadrants and a central scotoma (score 8) The atrophy score was 0 Full recovery was predicted Nine months following surgery there were relative field defects in two quadrants (score 2) Visual acuity had improved to 1 0 (+2 0 sph) There was a postoperative increase in atrophy Recovery therefore was poorer than predicted

Successful prediction of recovery is possible only if the degree of atrophy remains unchanged after surgery In our series atrophy was unchanged in all eyes but one (Case 3 left eye) A postoperative increase in atrophy may be caused by surgical trauma An alternative explanation could be that there is a delay of at least four weeks between time of axonal damage and appearance of signs of atrophy in the fundus (Lundstrom & Frisén 1975) In case 3 there was a history of very recent visual impairment before surgery Obviously a great deal of caution is necessary when trying to predict recovery *in* cases where deterioration of function occurs a few weeks prior to surgery In cases with *late* progression of atrophy (atrophy occurring after some eight weeks *or more after surgery*) descent of the chiasm into the sella (Mortara & Norrell 1970 Welch & Stears 1971) and tumour recurrence need to be considered

Fig 4 A B C

A Case 3 right eye Consult the text for details B Preoperative visual field examinations Score 9 C Postoperative visual field examinations Score 0 (The flat profile in static perimetry is presumably due to undercorrection of presbyopia)





Although atrophy was unchanged in 11 out of 12 eyes only five eyes showed improved visual fields after surgery Complete recovery occurred in only two eyes Most of the improvement occurred within two weeks after surgery as reported also by other investigators (Bakay 1950 Kayan & Earl 1975) The mechanisms underlying recovery of vision and their time course are poorly known (see Frisen et al 1976 for a recent review) but a more protracted recovery is empirically rare Our follow up intervals (8–12 months Table I) should be adequate in this regard

Pallor of the optic disc is a notoriously poor indicator of optic atrophy Considerable recovery of vision is possible even in cases with pale discs (Kayan & Earl 1975) The more extensive evaluation of nerve fibre atrophy used here allows much more accurate predictions 11 out of 12 predictions were correct

References

Bakay L (1950) *The results of 300 pituitary adenoma operations (Professor Herbert Olivecrona s series) J Neurosurg 7* 240–255

Frisén L Sjostrand J Norrsell K & Lindgren S (1976) Cyclic compression of the intracranial optic nerve patterns of visual failure and recovery Case report *J Neurol Neurosurg Psychiat 39* 1109–1113

Kayan A & Earl C J (1975) Compressive lesions of the optic nerves and chiasm Pattern of recovery of vision following surgical treatment *Brain 98* 13–18

Lundstrom M & Frisen L (1975) Evolution of descending optic atrophy A case report *Acta ophthal (Kbh) 53* 738–746

Lundstrom M & Frisen L (1976) Atrophy of optic nerve fibres in compression of the chiasm Degree and distribution of ophthalmoscopic changes *Acta ophthal (Kbh) 54* 623–640

Mortara R & Norrell H (1970) Consequences of a deficient sellar diaphragm *J Neurosurg 32* 565–573

Welch K & Stears J C (1971) Chiasmapexy for the correction of traction on the *optic nerves and chiasm associated with their descent into an empty sella turcica* Case report *J Neurosurg 35* 760–764

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ATROPHY OF OPTIC NERVE FIBRES IN COMPRESSION OF THE CHIASM

Observer Variation in Assessment of Atrophy

BY

MATS LUNDSTRÖM

Different observers assessment of atrophy according to a semi quantitative method was analysed Five observers scored the degree of atrophy on magnified black and white fundus photographs from normal controls and from patients with chiasmal lesions of different severity Four of the five examiners achieved a reasonably uniform assessment of atrophy The results of the test prompted some modifications in the grading system

Key words optic atrophy – optic chiasm – ophthalmoscopy – fundus photography

Lesions of the optic chiasm are usually associated with atrophic changes in the nerve fibre layer of the retina The degree and distribution of such changes are determined by the severity of chiasmal damage In a previous paper Lundstrom & Frisén (1976) described a method for semi quantitative assessment of nerve fibre atrophy The grading of atrophy was made on magnified black and white fundus photographs from patients with chiasmal compression due to chromophobe adenoma The aim of the present study was to analyse how different examiners evaluate the same fundus photographs Photographs showing normal fundi were included

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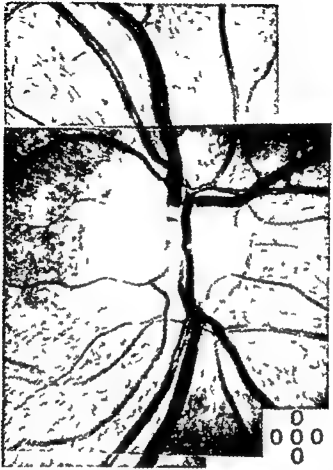

Fig 1
Demonstration photograph No 1 Normal appearance of the optic disc and the nerve fibre layer in all sectors Total atrophy score 0

Material and Methods

Magnified photographs were produced with the same technique as described in a previous paper (black and white negatives exposed through a red free filter and copied on photographic paper) (Lundstrom & Frisen 1976) The magnification was 40 x Six fundus photographs were selected from a series of patients with compression of the chiasm due to chromophobe adenoma (Figs 2–7 in Lundstrom & Frisen (1976)) Another six photographs were obtained from individuals without any known disease

Fig 2

Demonstration photograph No 2 Normal appearance of the nerve fibre layer in the upper and lower sectors Total atrophy in the temporal sector and partial atrophy in the nasal sector with correspondingly denuded disc borders Total atrophy score 4

Five ophthalmologists with from three to 10 years of clinical experience partook as observers They had not seen any of the patients or the fundus photographs before the test None had had any formal training in the ophthalmoscopic evaluation of the retinal nerve fibre layer

The examiners were provided with a written instruction identical to the section Grading of ophthalmoscopic signs of atrophy in Lundström & Frisen (1976) The grading system can be described briefly as follows

The appearance of the nerve fibre layer is evaluated in four peripapillary

Fig 3

Demonstration photograph No 3 Total atrophy in the horizontal sectors and partial atrophy above and below Pale optic disc with sharp borders in all directions
Total atrophy score 8

sectors temporal nasal above and below The optic disc is evaluated separately Normal appearance is given a score of 0 partial atrophy a score of 1 and total atrophy a score of 2 Scores are summed for each eye separately A normal nerve fibre layer and a normal disc score 0+0+0+0+0 = 0 a complete atrophy scores 2+2+2+2+2 = 10

The text was supplemented with three demonstration photographs (Figs 1–3) produced with the same technique as the test pictures The appearance of the

nerve fibre layer was scored by the author Every examiner had free access to the instruction and the scored demonstration pictures during the test

The test pictures were graded in sequence without any time limitations The four peripapillary sectors and the optic disc were graded separately in each picture and the total atrophy score was calculated The test was repeated after a minimum interval of two weeks under the same conditions but with an altered sequence of pictures No communication was allowed during the test and neither grading technique nor results were discussed before the second test was completed No information was given concerning the proportion of normal to abnormal pictures

Results and Discussion

The six pictures from normal individuals were considered by the author to show a prominent nerve fibre layer in all sectors The optic discs were also considered normal Every picture was graded twice by the five examiners resulting in 60 gradings A total atrophy score of 0 was given in 39 instances (= 65 %) A score of 1 was given in another 17 % and still higher scores in the remaining 18 % Each observer s average score per picture is shown in Fig 4 The diagram shows that only two or three pictures were easily recog

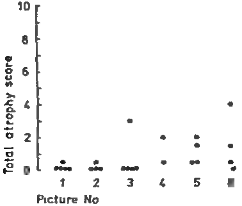

Fig 4

Total atrophy scores for test pictures Nos 1–6 (normal controls) Each dot represents the mean value of each observer s first and second grading

nized as being normal One and the same examiner (examiner E) is responsible for the two most aberrant scores and obviously had greater difficulty in recognizing a normal nerve fibre layer than the others

According to the grading system only a total score of 0 is regarded as normal However there are individual variations in the visibility of the retinal nerve fibre layer Also variation in observer assessment is unavoidable Therefore a summed atrophy score higher than 0 may be admissible in a clinically normal eye but this requires further study

The remaining six pictures were considered to show various grades of atrophy and were previously given atrophy scores ranging between two and nine (Lundstrom & Frisén 1976) Each observer s average score per picture is shown in Fig 5 together with the previous gradings These pictures were never given a total score of 0 in the test In three instances (= 5 %) a score of 1 was given

The examiners total scores were almost equal in some pictures (Nos 1 2 3 11 and 12) but showed moderate ranges in others (Nos 4 7 and 8) It is not possible to make any firm conclusions in this specially selected material but it appears that disagreements in the gradings were more evident in pictures showing partial atrophy

The relationship between the examiners average scores and the previously published scores is demonstrated in Fig 6 There was an obvious tendency

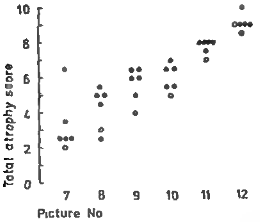

Fig 5

Total atrophy scores for test pictures Nos 7–12 (chiasmal lesions) Dots represent the mean values of each observer s first and second grading Open circles represent the previously published gradings

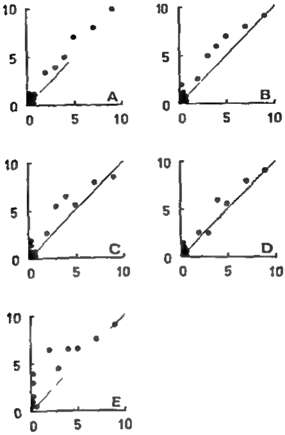

Fig 6

Relationship between the observers total atrophy scores (vertical axis) and the author s scores (horizontal axis) on pictures 1–12 Each observer (A E) is represented by a separate diagram each dot represents one case. The diagonals represent exact agreement.

among all the examiners to give a somewhat higher score than we did The overratings were not confined to any single area

Fig 7 shows the variation in reliability between the examiners The total atrophy scores from the first and the second gradings are plotted against each other for each observer The first and the second gradings agreed exactly 25 times out of 60 (= 42 %) The first and the second optic disc gradings agreed in 85 % compared with 70 % for the peripapillary sectors The results from the peripapillary gradings suggest an influence by the grade of atrophy In the

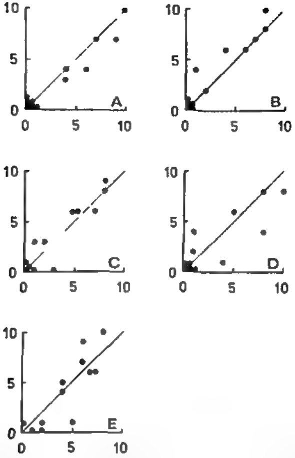

Fig 7

Relationship between the observers total atrophy scores from the first (horizontal axis) and the second (vertical axis) gradings Each observer (A E) is represented by a separate diagram each dot represents one case The diagonals represent exact agreement

case of normal peripapillary sectors the first and second gradings agreed in 80 % The corresponding figure for sectors with total atrophy was 73 % but only 56 % in cases with partial atrophy

Disparity within and between examiners was thus most obvious in peri papillary sectors showing partial atrophy This points to the need of better definitions in the scoring system In particular the sign of retinal mottling proved difficult to evaluate The term retinal mottling applies to the finely granular appearance of the fundus that occurs in cases with total atrophy of

Table I
Degrees of diffuse atrophy of the peripapillary nerve fibre layer

Score	Signs
0	Conspicuous obscuration by nerve fibre bundles of all but the largest vessels Conspicuous striation and nerve fibre opacity
1	Some obscuration by nerve fibre bundles of small vessels cross hatching present Some striation present Faintly visible nerve fibre opacity
2	No obscuration of vessels vessels narrow and pseudo sheathed Absence of striation and nerve fibre opacity

the nerve fibre layer (Lundstrom & Frisen 1975) However retinal mottling is more easily seen ophthalmoscopically than in photographic prints and should perhaps be excluded from the scoring system An attempt towards improved definitions is given in Tables I and II

The primary aim of the scoring system is to facilitate a uniform and reliable evaluation of the retinal nerve fibre layer by different examiners It demands concentration during the fundus examination upon the direct and indirect signs of nerve fibres in all peripapillary sectors (Tables I and II) Proper evaluation of these signs requires a certain degree of training In the present investigation

Table II
Degree and distribution of optic disc atrophy

Score	Signs
0	Optic disc borders finely blurred Optic disc with normal colour
1	Finely blurred upper and lower disc borders Sharply defined nasal and temporal disc borders
2	Sharply defined optic disc borders in all directions Marked pallor of the optic disc

the examiners stated spontaneously that it was easier to visualize and evaluate the nerve fibre layer in the second test This was also borne out by the fact that there was a smaller difference between the author s and the examiners scores in the second test (mean difference 1 2 points per picture in the first test vs 0 9 in the second)

It can be concluded that the appearance of the retinal nerve fibre layer was accessible to meaningful evaluation for at least four of the five examiners and that these four achieved a reasonably uniform assessment of atrophy

References

Lundstrom M & Frisen L (1975) Evolution of descending optic atrophy A case report. *Acta ophthal (Kbh)* 53 733–746

Lundstrom M & Frisen L. (1976) Atrophy of optic nerve fibres in compression of the chiasm Degree and distribution of ophthalmoscopic changes *Acta ophthal (Kbh)* *54* 623–640

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NORMAL VALUES IN CLINICAL ELECTROOCULOGRAPHY

III Numerical Evaluation of Two Dimensionless EOG Parameters

BY

ERIK KROGH

The distribution of the Arden ratio (A) and another dimensionless EOG quantity (G) devised by Gliem (1971) in a sample of normal human sub jects are presented The minimum median and maximum values for A are 148–241–449 and for G 34–88–167 A demonstrates a smaller degree of dispersion than G the latter resembling in this respect the EOG potential parameters of the same sample. The average accumulation of errors due to inaccurate assessment of the included potential figures is almost equal in the functions of A and G Divergencies between the figures from the present and earlier investigations are discussed together with the general advantage of dimensionless EOG parameters It is con cluded that the present investigation has not demonstrated the need to replace or supplement the Arden ratio by the Gliem quantity

Key words electrooculography – EOG – electrophysiology – dimension less parameters – Arden ratio – Gliem ratio – sample dispersion – estimate of error – Gauss principle

Both the inter and intra individual variation of EOG potentials are docu mented in many reports (François et al 1956 Davis & Shackel 1960 Arden & Barrada 1962 Muller & Haase 1970) Arden et al (1962) must be credited

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with the first attempt to devise a less variable EOG parameter The ratio between the extreme potential values (light peak (L) and dark trough (D)) recorded during 12 min of dark adaptation followed by 10 min of light adaptation provides information of the light induced potential rise and is independent of the poorly controlled distance between the voltage source and the skin electrodes The ratio is usually expressed as $\frac{L}{D} \times 100$ and is called the Arden ratio

François et al (1956) investigated the EOG potential drop following the interruption of a short light stimulus and expressed this parameter in μV as well as in units of the maximum potential value However closer scrutiny of their data reveals that the relative dispersion $\frac{s}{x}$ (Pearson s coefficient of variation) is not less for the dimensionless expression (0 33) than for the potential figure (0 27) The applied illumination sequence gave rise to a weak and sometimes negative light induced potential change and the authors later replaced it by the Arden scheme supplemented by a second dark adaptation (François et al 1966) A new dimensionless parameter was introduced which in terms of light peak and dark through is written as $\frac{L-D}{D}$ This quantity is however a simple transformation of the Arden ratio $(\frac{L}{D}-1)$ and consequently no new information or less dispersion is to be expected from it

Table 1

Distributions of the Arden ratios of normal human eyes as given by various authors

	Mean value	Range
Arden & Barrada (1969)	252 4	191–387
François et al (1966)	185*	139–235
Geijer Mannerfelt & Pallin (1968)	265	163–391
van Lith & Balik (1970)	2 15	not stated
Reeser et al (1970)	2 48	1 75–3 67
Adams (1973)	223 84	150–360

* In the original paper stated as 1/8

Table I summarizes the Arden ratio distributions from various normal samples The data in the five reports last referred to are obtained by using a version of the Arden technique A considerable and unexplained intra individual variation of the Arden ratio is demonstrated in other papers (Kelsey 1967 Muller & Haase 1970)

Gliem (1971) suggested that a further reduced dispersion would arise from the introduction of a reference value for the light and dark induced poten tial oscillations Consequently he recorded a base value B after 10 min of pre adaptation with the same light stimulus as applied later in the test (2000 lx) and continued according to the Arden scheme The proposed para meter was $\frac{L-D}{B} \times 100$ which together with its components $\frac{L}{B} \times 100$ and $\frac{D}{B} \times 100$ were analysed in both normal and pathological eyes The normal mean values and standard deviations of the three terms were $65 \pm 22\,\%$ $119 \pm 26\,\%$ and $55 \pm 17\,\%$

Thijssen & Pinckers (1970) introduced another dimensionless EOG para meter based upon the average voltage d recorded during an extended illu mination period (including two light peaks and one light trough) The dif ference between the first light peak and d was called a and the relative para meter was $\frac{a}{d}$ which in the authors experience yielded a better separation between normal and pathological eyes than the Arden ratio and the A criterion (a potential parameter calculated by subtracting fractions of an initial value and of the dark trough from the light peak value (Pinckers & Thijssen 1971))

The object of this paper is to present and discuss the frequency distributions of the Arden and Gliem quantities in a series of normal human subjects The sample dispersion of these two ratios is estimated and compared with that of the constituent potential figures Finally their stability against the inevitable small errors in the assessment of the potential terms included is evaluated by means of simple differential calculus

Material and Methods

The normal case series comprises 149 eyes (72 subjects with equal representation of females and males and an age span of 13–81 years) A detailed description of the sample and of the EOG technique is to be found in another paper (Krogh 1975) and an analysis of the potential parameters has been published (Krogh 1976) DC amplifi cation was used in order to obtain more reliable recorder deflections but on the other hand it meant that only 111 B values could be recorded

Average accumulation of errors

Gauss formula takes the following forms for the Arden and the Gliem quantities

$$2)\quad Pf_{(A)} = 100 \times \frac{\sqrt{\left[\frac{1}{D}\, dL\right]^2 + \left[\frac{-L}{D}\, dD\right]}}{\frac{L}{D}} \quad \text{and}$$

$$3)\quad Pf_{(G)} = 100 \times \frac{\sqrt{\left[\frac{1}{B}\, dL\right]^2 + \left[\frac{1}{B}\, dD\right] + \left[\frac{-(L-D)}{B^2}\, dB\right]}}{\frac{L-D}{B}}$$

The error in measuring the recorder deflections is estimated to a maximum of 4 μV (amplifier gain 20–40 μV/mm slide gauge with 0 05 mm divisions average of about ten deflections) It is reasonable to assume that $dB = dD = dL$, and that they are essentially alike for large and small deflections With this figure and the medians of B D and L as exemplifications the following values are calculated

4) $Pf_{(A)}$ = 1 8 % and

5) $Pf_{(G)}$ = 2 0 %

The corresponding errors in measurement of the potential parameters are $Pf_{(B)}$ = 1 1 % $Pf_{(D)}$ – 1 7 % $Pf_{(L)}$ = 0 7 % and $Pf_{(L\ D)}$ = 1 8 %

Discussion

The present Arden ratio distribution is characterized by a low central value (mean = 247) and an extended range as compared with the figures of Arden & Barrada (1962) Adams (1973) found significantly higher Arden ratios in the female part of his normal sample and noted a surplus of women in the series of Arden & Barrada (1962) Geijer Mannerfelt & Pallin (1968) and Reeser et al (1970) The large mean value in the study of Geijer Mannerfelt & Pallin (1968) is however also remarkable in view of the low stimulus intensity (100 lx) Similarly the small mean value in the investigation of van Lith & Balik (1970) was attributed to an excess of men in the sample These connexions in the present series will be examined in a following paper

The upper limit of the Arden ratio range reflects the degree of saturation of the light sensitive voltage source which is maximal at an illuminance of $\gtrsim$ 10 000 Trolands (Arden & Kelsey 1962a b) as employed in the present EOG procedure The main group of Arden & Barrada (1962) was exposed to 3000

Trolands A sufficient length of the dark period is also important for the following light rise In the EOG technique of Arden & Barrada (1962) the subject was kept in darkness for 12 min whereas the present procedure operates with variable dark periods extending to the moment when the dark troughs are passed with certainty in both eyes (14–20 min)

The extended test of François et al (1966) gave low normal values for the Arden ratio although the dark period was 15 min and the stimulus luminance was 5000 cd/m² The Arden ratios were computed from the second dark trough which separates them from those of the above mentioned samples The parameter $\frac{L-D}{D}$ is however derived from the first dark trough which allows a calculation of the Arden ratio from the same part of the test When this is done no significant difference between these two sets of Arden ratios is detectable (Mann Whitney s test $P > 0.1$) The data were collected from 20 normal eyes without specification and therefore sample characteristics influencing the frequency distribution as outlined above cannot be excluded

The range of the Gliem ratio in the original paper (Gliem 1971) is approximately 20–140 and the larger mean value and the upward shifted range in the present investigation are explained by its larger relative light rise This is also illustrated by the small Arden ratio which results from Gliem s figures for the mean relative potential rise and drop ($\frac{1.19}{0.55} \times 100 = 216$) One possible reason for this discrepancy is that 78 of the 150 eyes in Gliem s normal sample in fact stemmed from a pathological population although the disease was clinically unilateral Also the different measuring intervals (2–3 min in Gliem s technique 1 min in the present) may give rise to different assessments in particular of the light peaks since the rate of voltage change is quite high in this part of the test

Quantitative statements of the reduced dispersion provided by the dimensionless EOG parameters are not to be found in the earlier literature Arden & Barrada (1962) refer to the different form of the log $\frac{x}{\bar{x}}$ histograms of the potential parameters and the Arden ratio From Gliem s data it is possible to calculate some $\frac{s}{\bar{x}}$ values For B it is 0.41 for the relative light rise and dark drop it is 0.22 and 0.31 respectively and for their difference a value of 0.34 is obtained

In the present material the dispersion of the Gliem ratio appears to be larger than that of the Arden ratio which is in keeping with the larger dispersion of B and $L-D$ as compared with D and L According to Kolder (1959) a reason

ably stable base value requires at least 60 min of constant illumination The Gliem ratio appears to offer no advantages over the potential parameters in this respect but once more the lack of significance tests in this context is emphasized According to the error analysis the two dimensionless EOG para meters show an almost identical stability against errors in potential measure ment. By multiplication of the potential symbols in the Gauss formulae (2) and (3) for A and G respectively by a constant it is seen that the error level increases with decreasing potential level

To summarize the present study of a normal sample has not proven the need to supplement or replace the simple and well known Arden ratio by the Gliem ratio It cannot be totally excluded that a different result would be obtained if a number of eyes with relevant pathology were investigated although this seems unlikely The present analysis has indicated a moderate reduction of the data dispersion when the EOG potential figures are replaced by the Arden ratio and this advantage must be weighed against the possible loss of relevant information contained in the complete voltage time curve A dimensionless parameter is however necessary for reliable comparison of data recorded with different electrode amplifier or display equipment, since the potential figures are too dependent upon the technical specifications of the recording

List of abbreviations

B = base value recorded after 10 min of pre adaptation
D = dark trough the lowest potential during dark adaptation
L = light peak, the largest potential during illumination
$L-D$ = the light induced potential rise.

A = the Arden ratio = $\frac{L}{D} \times 100$

G = the Gliem ratio $\frac{L-D}{B} \times 100$

Pearson's coefficient of variation = $\frac{s}{\bar{x}}$

CV = a percentile based coefficient of variation = $\frac{\text{90 percentile} - \text{10 percentile}}{\text{median}}$

Pf = the average accumulation of errors in a function, f comprising n variables estimated by Gauss formula

$\Delta f = \sqrt{\sum_{r=1}^{n}}$ (differential of f in relation to r) divided by f and expressed as a percentage.

References

Adams A (1973) The normal electro oculogram (E O G) *Acta ophthal (Kbh)* 51 551–561

Arden G B Barrada A & Kelsey J H (1962) New clinical test of retinal function based upon the standing potential of the eye *Brit J Ophthal* 46 449–467

Arden G B & Barrada A (1962) Analysis of the electro oculograms of a series of normal subjects *Brit J Ophthal* 46 468–482

Arden G B & Kelsey J H (1962) Changes produced by light in the standing potential of the human eye *J Physiol (Lond)* 161 189–204

Arden G B & Kelsey J H (1962) Some observations on the relationship between the standing potential of the human eye and the bleaching and regeneration of visual purple *J Physiol (Lond)* 161 205–226

Davis J R & Shackel B (1960) Changes in the electro oculogram potential level *Brit J Ophthal* 44 606–618

Defares J G Sneddon I N & Wise M E (1973) *An introduction to the mathematics of medicine and biology* 2nd ed North Holland Publishing Company Amsterdam London

François J Verriest G & de Rouck A (1956) Electro oculography as a functional test in pathological conditions of the fundus II Base value and drop during dark adaptation. *Brit J Ophthal* 40 305–312

François J de Rouck A Verriest G & Szmigielski M (1966) An extended clinical test of the ocular standing potential and its results in some cases of retinal degeneration *Proceedings of the 4th ISCERG Symposium Jap J Ophthal 10 (Suppl)* 257–263

Geijer Mannerfelt T & Pallin O (1968) On the correlation between ERG and EOG in normal eyes In Schmoger E Ed *Electrophysiology and pathology of the Visual System Proceedings of the 6th ISCERG Symposium* pp 47–51 VEB Georg Thieme Leipzig

Gliem H (1971) *Das Elektrookulogramm Ein Erfahrungsbericht* Abhandlungen aus dem Gebiete der Augenheilkunde Band 40 VEB Georg Thieme Leipzig

Kelsey J H (1967) Variations in the normal electro oculogram *Brit J Ophthal 51* 44–49

Kolder H (1959) Spontane und experimentelle Änderungen des Bestandpotentials des menschlichen Auges *Pflugers Arch ges Physiol 268* 258–272

Krogh E (1975) Normal values in clinical electrooculography I Material method, methodological investigations and distribution of the potential and time parameters *Acta ophthal (Kbh) 53* 563–575

Krogh E. (1976) Normal values in clinical electrooculography II Analysis of potential and time parameters and their relation to other variables *Acta ophthal (Kbh) 54* 389–400

van Lith G H M & Balik J (1970) Variability of the electro oculogram (EOG) *Acta ophthal (Kbh) 48* 1091–1096

Muller W & Haase E (1970) Inter und intraindividuelle Streuung im EOG *Albrecht v Graefes Arch klin exp Ophthal 181* 61–68

Pinckers A & Thijssen J (1971) The A criterion in electro oculography In Basar D and Bengisu U Eds *Proceedings of the VIIth ISCERG Symposium* pp 284–288 Faculty of Medicine Istanbul

Reeser F Weinstein G W Feiock K B & Oser R S (1970) Electro oculography as a test of retinal function *Amer J Ophthal* *70* 505–514

Thijssen J & Pinckers A (1970) System analysis of the human electro oculogram In Wirth A Ed *Proceedings of the VIIIth Symposium of ISCERG* pp 314–319 Pacini Pisa

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PATHOGENESIS OF UNILATERAL PROPTOSIS

BY

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A series of 34 patients presenting with unilateral proptosis has been studied in order to evaluate the mechanism of proptosis It is observed that symmetrical (axial) proptosis is usually the result of generalised increase in intraorbital contents and occurs in thyroid disease and with intracranial lesions lying remote from the orbit Rarely in myasthenia gravis it may be caused by myogenic paralysis of the extraocular muscles Asymmetrical proptosis is the result of localised increase in intraorbital contents and this occurs with expanding lesions of the orbit and in lesions arising from neighbouring structures and enroaching the orbit

Key words unilateral proptosis – exophthalmos – space occupation – venous stasis – extraocular muscle weakness – pathogenesis

When an eye is proptosed the direction of proptosis may be directly forward and this is called symmetrical (axial) proptosis or it may deviate up or down or to either side and this is called asymmetrical proptosis This condition has long been recognised as a manifestation of various underlying conditions the frequency of which has varied according to the interest of the authors and has been described by O Brien & Leinfelder (1934) Dixon (1941) Drecher & Benedict (1950) Van Buren et al (1957) Bullock & Reeves (1959) Schultz et al (1961) Pohjola (1964) Zakharia et al (1972) Choudhury (1973) and many others

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The investigation and management of patients with unilateral proptosis are mainly the responsibility of the ophthalmic surgeon but commonly require the close co operation of various other specialties Neurosurgeons are involved in the treatment of those lesions which spread from or are liable to spread into the cranial cavity Surgical exploration of the orbit for tumour may call for simultaneous exploration of the anterior or middle cranial fossae Not infrequently the causative lesion lies intracranially in a site remote from the orbit and in such a situation intracranial exploration is necessary

Despite the presence of extensive literature on th eaetiology and pathology of this condition there are relatively few references as regards its pathogenesis For this reason a careful review of 34 consecutive cases of unilateral proptosis has been undertaken in order to establish the pathogenesis

Clinical Material and Methods

From April 1971 to July 1978 34 patients with unilateral proptosis were studied in the Department of Neurosurgery at the Aberdeen Royal Infirmary Careful history taking thorough general medical and detail ophthalmological examinations of the patients and correlation with the findings of routine and special investigations operative findings and autopsy findings in fatal cases form the basis of this study the object of which is to evaluate the pathogenesis of unilateral proptosis For this reason only cases with an exophthalmometric reading in excess of 2 mm were included the non effected eye having been considered normal All measurements were made by the Hertel Exophthalmometer Cases with bilateral involvement even if they manifested such an exophthalmometric difference were not considered The ophthalmological examinations comprise inspection of the eyes palpation including resistance of the globes to pressure movements of the extraocular muscles measurements of the proptosis and intraocular tension and fundoscopy Forced duction test was not done Photographs of the eye haematological examination including full blood count ESR WR and serum calcium Mantoux test and plain radiographs of the orbit skull paranasal sinuses and chest were the routine investigations Photographs including postoperative ones were essential to form a base line and for future reference Plain radiographs were the most valuable investigations in diagnosing the nasal lesions and were helpful in others Other special investigations were selected on the merit of the individual case and thyroid function studies were done in suspected cases of endocrine proptosis Carotid angiography was the most commonly performed and useful investigation in most cases other than traumatic orbital lesion and endocrine proptosis Orbital

venography was done in orbital lesions and orbital pneumography in lesions suspected of arising from optic nerve and at times for extraconal lesions Brain scan was done for intracranial lesions and myodil ventriculography in cerebellar lesions Histopathological examinations of the tissue removed at operation and autopsy findings in fatal cases established the final diagnosis in neoplastic lesions Ultrasonography of the orbits and computerized axial tonography of the orbits or brain were not done B scan ultrasonography is available in specialised eye hospitals only It is invaluable in the investigation of orbital soft tissue masses their detection and differentiation EMI scanning is now available in larger neurosurgical centres It has proved promising in the investigation of intracranial and orbital disease It compliments the existing non invasive procedures and orbital venography in the investigation of orbital disease

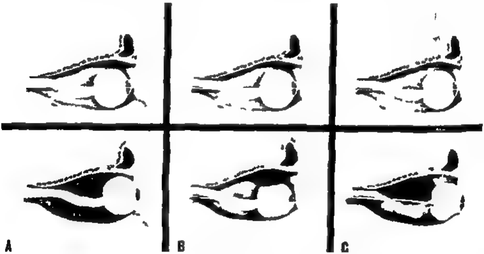
Table I
Analysis of 34 cases of unilateral proptosis studied

Site of lesion	No of cases	Type of lesion
Orbital	9	Metastatic tumour (4) Retrobulbar haematoma associated with fracture of roof of orbit (3) Optic nerve glioma (1) Ocular myasthenia (1)
Nasal	4	Empyema of ethmoid (1) Nasopharyngeal carcinoma (1) Carcinoma of maxillary antrum (1) Sarcoma of maxilla (1)
Orbito cranial	12	Carotid cavernous fistula (4) Intracavernous carotid aneurysm (3) Posterior communicating aneurysm (1) Cavernous sinus thrombosis (1) Pituitary adenoma (1) Sarcoma of pituitary fossa (1) Sphenoidal ridge meningioma (1)
Cranial	6	Subarachnoid haemorrhage (4) Subdural haematoma (1) Medulloblastoma (1)
Endocrine	3	Thyroid disease (3)

(Wright et al 1975) Wider availability and use of EMI scanning may eliminate the need for orbital pneumography and pneumo encephalography which are not only unpleasant but also not without risks

Analysis of the Series

The patients were divided into categories according to the site of the lesions Table I shows the groups and the type of lesion in each group Sites of the lesions for a table of this sort are defined essentially on the basis of causation of proptosis and are arranged as follows (1) orbital – those lesions that arise from the structures in the orbit including its bony walls Neoplastic lesions may arise primarily in the orbit or may extend into the orbit either by invasion from the surrounding structures or as a metastatic deposit Trauma to the orbit can produce retrobulbar haematoma which may or may not be associated with fracture of the roof of the orbit Myogenic paralysis of the external ocular muscles of the eyeball also falls into this group (2) nasal – these lesions



A B C

Fig 1

Schematic drawing of six sagittal sections of orbit showing variation in the degree and direction of proptosis in lower sections in comparison to the normal upper sections Lower sections (A) showing mild degree of proptosis and displacement of the eyeball directly forwards by generalised increase in intra orbital contents and diffuse space occupation (B) showing mild degree of proptosis and the displacement of the eyeball downwards by an anteriorly placed localised space occupying lesion and (C) showing *marked degree of proptosis and displacement of the eyeball downwards by a posteriorly* placed localised space occupying lesion.

Fig 2

Left sided proptosis due an empyema of the left ethmoid (A) photograph of the eyes showing displacement of the left eyeball temporally (B) tomogram of the paranasal sinuses showing lesion extending from the left ethmoid into the orbit and encroaching on the left nasal cavity and left frontal sinus (C) A P view of the orbital venogram showing displacement upwards and outwards of the first and second segments of the venous parallelogram on the left and (D) orbital pneumogram showing outward displacement of the eyeball by expansion of the left ethmoid into the orbit

comprise those of the nasal cavity nasopharynx and the paranasal sinuses (3) orbito cranial – those lesions that arise in or about the cavernous sinus and sphenoidal ridge (4) cranial – those intracranial lesions that are remote from the orbit (5) endocrine – this is grouped separately because the proptosis here is the localised manifestation of a generalised disorder

There were three patients in this group all due to thyroid diseases They were referred to us for excluding other underlying pathology because their thyroid function tests were normal

Discussion

Proptosis is the forward displacement of the eyeball in relation to the skull It may occur due to space occupation in the orbit from lesions arising in the orbit or lesions encroaching from the neighbouring structures Such space occupation may result from a localised or from a generalised expanding lesion Secondary venous stasis in the orbit may produce oedema and congestion of the orbital tissues which may displace the eyeball forward Lastly instability of the eyeball may occur from weakness of the external ocular muscles and this may lead to proptosis

Space occupation

A localised expanding lesion in the orbit may arise from its walls from the intraobital contents or as an invasion from the neighbouring structures The effect of such a lesion will depend upon its site and size An anteriorly placed lesion (Fig 1 B) displaces the eyeball up or down or to either side and pro duces a mild to moderate degree of proptosis Fig 2 illustrates such a case

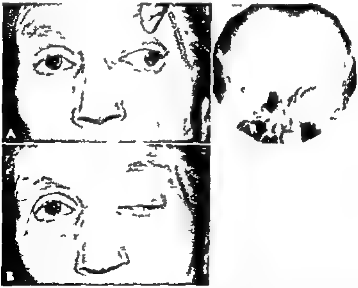


Fig 2

Left sided proptosis due to a left sphenoidal ridge meningioma (A) photograph on the eyes showing displacement of the left eyeball temporally and downwards (B) photo graph of the eyes showing marked ptosis on the left side and (C) plain radiograph of the orbit, showing increased bone density of the sphenoidal bone on the left side and widening of the left superior orbital fissure

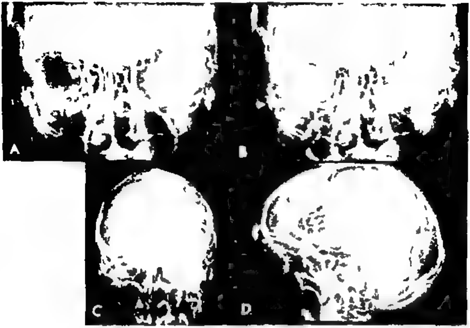


Fig 4

A P views of orbital venograms (A) early phase showing displacement of the superior ophthalmic vein medially and upwards in the left orbit and (B) late phase of the venogram showing delayed emptying of the superior ophthalmic vein on the left compared to the right indicating obstruction of the posterior venous drainage of the orbit due to sphenoidal ridge meningioma (C) A P view of the left carotid angiogram showing upward and inward displacement of the middle cerebral group of arteries and (D) lateral view showing upward displacement of the middle cerebral group and enlargement of the ophthalmic artery indicating a sphenoidal ridge meningioma with its extension into the orbit

caused by an empyema of the left ethmoid extending into the orbit It produced a left sided proptosis of 11 mm and displacement of the eyeball temporally (Fig 2 A) Fig 2 B C and D show the expansion of the ethmoid

A posteriorly placed orbital lesion (Fig 1 C) also displaces the eyeball away from its axis and produces a greater degree of proptosis This is due to contributory additional factors such as venous stasis in the orbit and extraocular muscle weakness due to pressure on the 3rd 4th and 6th cranial nerves at the superior orbital fissure Figs 3 and 4 illustrate such a case caused by an orbito cranial meningioma arising from the left sphenoidal ridge It produced a left sided proptosis of 15 mm and displacement of the eyeball temporally and

downwards (Fig 3 A) and marked ptosis (Fig 3 B) Figs 3 C and 4 A B C D show the presence of a left sided orbito cranial mass lesion

Intraconal expanding lesions lying immediately behind the eyeball have been reported to cause symmetrical proptosis (Dixon 1941 Wright 1970) In our experience these lesions displace the eyeball either vertically or horizontally because of their origin from one or the other side of the optic nerve Fig 5 illustrates such a case caused by a right intraorbital optic nerve glioma It produced a right sided proptosis of 5 mm and showed displacement of the eyeball temporally (Fig 5 A)

Fig 5 B shows the retrobulbar mass lesion and Fig 5 C confirms the diagnosis

Diffuse space occupation may occur in the orbits in thyroid disease and this is the commonest cause of both unilateral and bilateral proptosis (Smith 1967 Wright 1970) Here the globe is displaced directly forward (Fig 1 A) because of the generalised deposition of hydrophilic mucopolysaccharide throughout the orbital tissue hence the proptosis is often symmetrical The unilateral nature of the proptosis depends upon the relative increase in intraorbital content in one or the other orbit A highly selected group of these cases are referred for

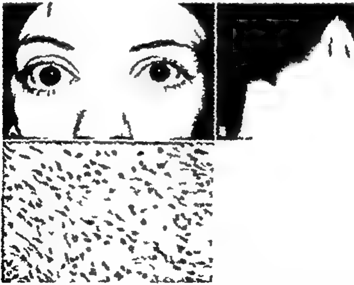


Fig 5

Right sided proptosis due to right intraorbital optic nerve glioma (A) photograph of the eyes showing displacement of the right eyeball temporally (B) orbital pneumogram showing the dumbell shaped enlargement of the optic nerve and (C) photomicrograph showing a well differentiated fibrillary astrocytoma

Fig 6

Left carotid angiogram A P view showing a large subdural haematoma with displacement of the anterior cerebral artery to the right side and calcification in the falx cerebri in the midline

special investigation in order to exclude any underlying localised space occupying lesion These cases comprise those who are clinically euthyroid and in whom thyroid function tests are either normal or non contributory Three such cases were encountered in the present series In them the diagnosis was established because of the symmetrical nature of the proptosis absence of difference in exophthalmometric readings taken in sitting and supine positions – Hauer s sign – and a normal orbital venogram

Venous stasis

Unilateral proptosis when it is caused by venous stasis alone is the result of relative increase in intraorbital contents and is found in intracranial lesions lying remote from the orbit Such lesions may cause intracranial hypertension which in turn produce increased intracranial venous pressure This is transmitted from the cranial cavity to the orbital veins resulting in orbital venous

stasis consequent venous congestion and oedema of the orbital tissue produce an increase in orbital contents and proptosis The unilateral nature of the proptosis is very dependent upon the pattern of the venous drainage from the cavernous sinus which forms the final common pathway for antegrade and retrograde venous flow from and to the orbit respectively The venous system is remarkably variable The cavernous sinue may fail to develop on one side or the other (Hamby 1966) or the venous drainage of one sinus may predominantly be into the other side (Pool & Potts 1965) The side of dominance of venous drainage from the cavernous sinus probably determines the side of the proptosis but proptosis tends to be symmetrical in this type of case (Fig 1 A)

Davidoff & Dyke (1938) and Pfeiffer (1943) described cases of unilateral exophthalmos from relapsing juvenile chronic subdural haematomas The proptosis was due to deformity of the lateral orbital wall with its convexity inwards and thus compromising the orbit Gardner (1948) described a case of unilateral exophthalmos which was due to raised intracranial pressure occurring in a haemangiomatous cyst of the cerebellum in this case the exophthalmos was caused by an encephalocele in the orbit through its roof which had been absorbed following a previous fracture

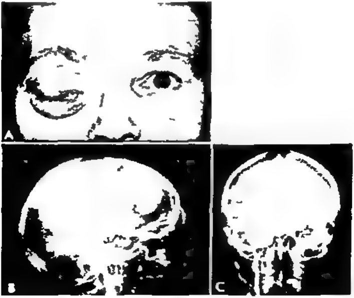


Fig 7

Right sided proptosis due to right carotid cavernous fistula (A) photograph of the eyes showing congested and oedematous eyelids and complete ptosis (B) lateral view and (C) A P view of right carotid angiogram showing the early filling of the cavernous sinus and distended ophthalmic veins

Fig 8

Right sided proptosis due to an unruptured right posterior communicating aneurysm (A) photograph of the eyes showing mild degree of right sided proptosis (B) photograph of the eyes showing complete ptosis on the right side (C) lateral view and (D) A P view of right carotid angiogram showing the posterior communicating aneurysm It also shows an internal carotid bifurcation aneurysm

Two such cases were encountered in the present series Chronic subdural haematoma in one and a cerebellar tumour in the other were the causes of unilateral proptosis There was no mechanical defect in the walls of the orbit Venous stasis in the orbit consequent to raised intracranial pressure was presumably the factor responsible for the causation of proptosis Fig 9 shows a left chronic subdural haematoma which caused a symmetrical proptosis of 7 mm on the left side

Proptosis of sudden onset may occur in acute intracranial hypertension as a result of orbital venous stasis (Duke Elder & Scott 1971 Choudhury 1975) As a rule the proptosis is bilateral in this condition During this study four of the 88 cases of spontaneous subarachnoid haemorrhage had unilateral proptosis Association of haemorrhage into the extraocular orbital tissues and optic nerve sheath has been reported in such cases (Walsh & Hedges 1951 Muller & Deck 1974) and may be a contributory factor

Venous stasis unassociated with intracranial hypertension is the dominant

factor in the genesis of proptosis in lesions situated medially in the orbito cranial junction In these conditions neurogenic weakness of the extraocular muscles acts as a contributory factor and here the proptosis is usually asym metrical Retrograde venous flow in the orbit with consequent stasis occurs in cavernous sinus lesions Fig 7 illustrates such a case caused by a right carotid cavernous fistula This produced a right sided proptosis of 11 mm complete ptosis and gave rise to congested and oedematous eyelids (Fig 7 A) Fig 7 B and C show the fistula and the orbital venous stasis Pituitary adenomas may produce exophthalmos due to venous stasis (Dixon 1941 Meadows 1944) and intracranial carotid aneurysms may produce similar changes presumably by venous stasis (Jefferson 1937) Fig 8 illustrates such a case caused by an un ruptured right posterior communicating aneurysm It produced a right sided proptosis of 3 mm (Fig 8 A) complete ptosis (Fig 8 B) and displaced the eye ball temporally Fig 8 C and D show the aneurysm Other tumours in the pituitary fossa may produce proptosis due to venous stasis Figs 9 and 10 illustrate such a case caused by a sarcoma arising from the pituitary fossa It produced a left sided proptosis of 4 mm (Fig 9 A) complete ptosis (Fig 9 B) and nasal displacement of the eyeball (Fig 9 C) Fig 10 shows the mass lesion of the pituitary fossa

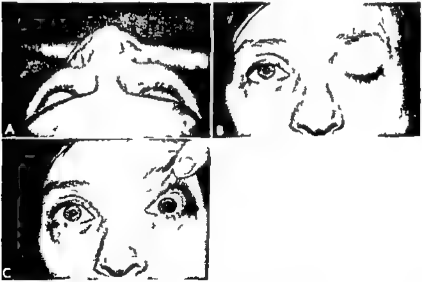


Fig 9

Left sided proptosis due to a sarcoma of the pituitary fossa Photographs of the eyes (A) showing mild degree of left sided proptosis (B) showing complete ptosis on the left side and (C) showing dilatation of the pupil and displacement of the eyeball nasally on the left side

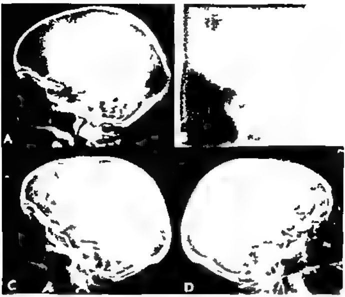


Fig 10

(A) plain radiograph of the skull lateral view showing complete destruction of the pituitary fossa (B) Tomogram of the pituitary fossa showing complete destruction of the pituitary fossa with extention into the sphenoidal bone (C) Lateral view of the left carotid angiogram showing pronounced upward stretching of the carotid syphon, and (D) lateral view of the right carotid angiogram showing slight upward stretching of the carotid syphon indicating a destructive mass lesion in the pituitary region

Eyeball instability

This occurs with paralysis of the external ocular muscles Neurogenic paralysis or weakness is a common occurrence and contributes to the other factors i e space occupation and venous stasis in the causation of proptosis Rarely myogenic paralysis of the muscles alone may lead to proptosis This is seen in some cases of myasthenia gravis – though as a rule proptosis in this condition is bilateral Unilateral proptosis in this condition had been reported (Dixon 1941) In his series there were three cases of ophthalmoplegia which showed unilateral exophthalmos Here the flaccidity of the ocular muscles allows orbital fat to push the eyeball forward and the proptosis as a rule is symmetrical Fig 11 illustrates such a case with a right sided symmetrical proptosis of 3 mm and bilateral partial ptosis (Fig 11 A) There was improvement in ptosis (Fig 11 B) and movement of the eyeball (Fig 11 C and D) after the injection of a test dose of Tensilon

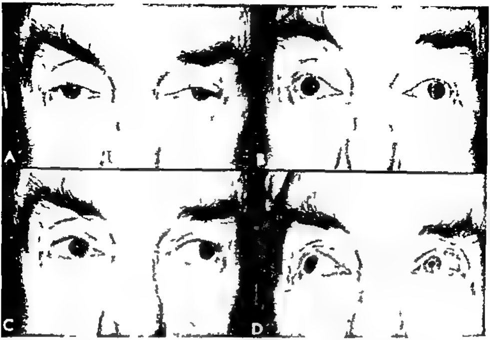


Fig 11

Right sided proptosis due to ocular myasthenia Photograph of the eyes (A) showing bilateral partial ptosis and after injection of a test dose of Tensilon showing (B) improvement in ptosis (C) movement of the eyeballs towards the left and (D) movement of the eyeballs towards the right

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References

Bullock L F & Reeves R J (1959) Unilateral exophthalmos Roentgenographic aspects *Amer J Roentgenol 82* 290–299

Choudhury A R (1973) Non endocrine Unilateral Proptosis *Trans ophthal Soc U K 93* 643–652

Choudhury A R (1975) Sudden onset of bilateral symmetrical proptosis in acute intracranial hypertension. *Amer J Ophthal 80* 85–87

Davidoff L M & Dyke C G (1938) Relapsing Juvenile Chronic Subdural Haematoma *Bull Neurol Inst N Y* 7 95–111
Dixon G J (1941) Unilateral Exophthalmos (proptosis) Causation and differential diagnosis *Brain 64* 73–89
Duke Duke Elder S & Scott G I (1971) Neuro Ophthalmology In Duke Elder S Ed *System of Ophthalmology* Vol 12 Disturbances of the circulation pp 23–32 Henry Kimpton London
Drescher E P & Benedict W L (1950) Asymmetric Exophthalmos *AMA Arch Ophthal 44* 109–128
Gardner W J (1948) Unilateral Exophthalmos due to Cerebellar Tumour and Orbital Defect *J Neurosurg 5* 500–502
Hamby W B (1966) *Carotid Cavernous Fistula Anatomy of Carotid Cavernous Fistula* pp 25–34 Charles C Thomas Springfield Illinois
Hauer J (1969) Additional Clinical Sign of Unilateral Endocrine Proptosis *Brit J Ophthal 53* 210–211
Jefferson G (1937) Compression of Chiasma Optic Nerve and Optic Tracts by Intracranial Aneurysms *Brain 60* 444–497
Meadows S P (1944) Orbital Tumours *Proc roy Soc Med 38* 591–600
Muller P J & Deck J H N (1974) Intraocular and Optic Nerve Sheath Haemorrhage in Cases of Sudden Intracranial Hypertension *J Neurosurg 41* 160–166
O Brien C S & Leinfelder P J (1934) Unilateral Exophthalmos *Trans Amer ophthal Soc 39* 324–340
Pfeiffer R L (1943) Roentgenography of Exophthalmos with Notes on the Roentgen Ray in Ophthalmology Part III *Amer J Ophthal 26* 928–941
Pohjola S (1964) Unilateral Exophthalmos with Special Reference to Endocrine Exophthalmos and Pseudotumour *Acta ophthal (Kbh) 4* 456–464
Pool J L & Potts D G (1965) Aneurysms and Arteriovenous Anomalies of the Brain Diagnosis and Treatment *Carotid Cavernous Aneurysms or Fistulas* pp 306–325 Harper and Row New York
Schultz R O Richards R D & Hamilton H E (1961) Asymmetric Proptosis *Amer J Ophthal 59* 10–15
Smith M E (1967) The Differential Diagnosis of Unilateral Exophthalmos *Int ophthal Clin 7* 911–933
Van Buren J M Poppen J L & Horrax G (1957) Unilateral Exophthalmos A Consideration of Symptom Pathogenesis *Brain 80* 139–174
Walsh F B & Hedges T R (1951) Optic Nerve Sheath Haemorrhage The Jackson Memorial Lecture *Amer J Ophthal 34* 509–527
Wright J E (1970) Proptosis *Ann roy Coll Surg Engl 0* 323–334
Wright J E Lloyd G A S & Ambrose J (1975) Computerized axial tonography in the detection of orbital space occupying lesions *Amer J Ophthal 80* 78–84
Zakharia H S Asdourian K & Matta C S (1979) Unilateral Exophthalmos Aetiological study of 85 cases *Brit J Ophthal 6* 678–686

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INCIDENCE OF UVEITIS IN NORTHERN FINLAND

BY

RAUNO MIETTINEN

The incidence of uveitis was studied among the 613 426 inhabitants of northern Finland in the year 1969 120 new cases of uveitis were found with a total incidence rate of 19 6 per 100 000 population The incidence was high in the age groups 20–59 years but low in the young and in older patients The onset of uveitis was independent of seasonal changes and the occupation of the patients The aetiology of uveitis remained undetermined in 81 %of cases Of the 120 patients 105 had anterior 10 posterior and 5 generalized uveitis The high incidence of anterior uveitis was in accordance wit the high frequency of the histocompatibility anti gen B27 among Finns

Key words epidemiology – aetiology – incidence – population survey – uveitis survey

There are few studies on the epidemiology of uveitis where the composition of the population at risk is presented (Darrell et al 1962) In northern Finland all uveitis patients are treated in the wards or outpatients departments of the eye hospitals and it is thus possible to correlate the cases of uveitis with the population at risk This paper presents the epidemiology of new cases of uveitis drawn from the population of northern Finland during one year

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Material and Methods

The records of all new uveitis patients residing in northern Finland in the year 1969 were reviewed The year 1969 was selected for the following reasons A good retrospective view was possible – there were neither major epidemics nor unexceptional changes of climate in 1969 – general practitioners no longer treated uveitis but instead referred the patients to eye hospitals – only 3 eye hospitals treated uveitis patients in 1969 in northern Finland more recently new eye hospitals have been established which would make such a study more complicated – on the basis of the 19 0 census it was possible to get exact corrected population statistics from the year 1969 – the large changes in the structure of population taking place nowadays caused by urbanization emigration and diminution of birth rate were only just beginning in 1969

Northern Finland is situated between 63 30 and 70° 5 northern latitude and it comprises the provinces of Oulu and Lappi Northern Finland is over 700 km long and its area is 160 344 km The period of permanent sunshine in the far north is 73 days and in winter the sun is absent for 51 days There is sunshine in the southmost part of northern Finland in June for 20 h a day and in December 4 h a day In Oulu the average temperature (centrigrade) is in January –9 5° in July +16 6° and during the whole year +2 3° Precipitation is annually about 0 5 m (Suomi kasikirja 1968)

At the end of the year 1969 the population of northern Finland was 613 426 with sex distribution of 309 70? males and 303 721 females The total population of the 10 urban communes of northern Finland was 204 691 while 408 735 people had rural residence Only in three towns (Oulu Kemi Rovaniemi) was the number of residents above 20 000 (Central Statistical Office of Finland 1973)

According to the 1970 census the population depended on agriculture (including forestry hunting and fishing) in 26 % on building construction in 11 % and on transport in 7 % These occupational groups comprised 44 % of the whole population and the work was mainly physical and occurred in the open air 14 % *of people were dependent* on industry Thus about 58 % of the residents of northern Finland depended on manual labour in which the risk of eye injuries is relatively high The rest 42 % of people depended on non manual work (Population census 1970)

In 1969 the inhabitants of northern Finland were served by the eye hospitals of Oulu Rovaniemi and Kajaani Outside the hospitals there were five private ophthalmic medical practitioners They as well as general practitioners always referred uveitis patients to eye hospitals without any treatment and

also the later follow up of patients was carried out by the outpatients departments of the eye hospitals

The present material was collected from the three eye hospitals of northern Finland All the cases of uveitis were diagnosed and treated by ophthalmologists in some of these three eye hospitals The material covered only those patients whose first onset of endogenous uveitis was during 1969 The cases of uveitis with traumatic origin were excluded The uveitis patients whose residence was outside northern Finland were also excluded from the material

The cases were divided into anterior posterior and generalized uveitis according to criteria used by Perkins (1961) The patient material was also classified on an aetiological basis by criteria used by Saari et al (1975)

Data on sex age diagnostic group aetiological diagnosis time of admission occupation and residence were coded for computer analysis

The patient material was divided into age groups and the incidence rates of uveitis per 100 000 population were calculated Corrected population statistics for the year 1969 were used in the calculations The corrections were made with the aid of the 1970 census (Central Statistical Office of Finland 1973)

The data were processed by computer at the Department of Automatic Data Processing University of Oulu The computer was a Univac 1108 and the programme used was HYLPS

The frequency differences were tested by the chi square test The significance was determined as follows $P < 0.05$ was almost significant and $P < 0.01$ was significant and $P < 0.001$ was highly significant

Results

There were 120 new uveitis patients in northern Finland in 1969 Table I shows their distribution in age groups incidence rates per 100 000 population and the population at risk in 1969 in northern Finland

31 males and 11 females had outdoor occupations The incidence of uveitis rose to a maximum in the age group 40–49 years both in males and in females The incidence was a little higher in females than in males in the age group 0–29 years Differences in the incidence rates between sexes were not statistically significant in any age group (Table II)

Uveitis was anterior in 105 (88 %) posterior in 10 (8 %) and generalized in 5 (4 %) Anterior uveitis became chronic in five patients during the observa

Table I

Age groups of new uveitis patients and incidence rates per 100 000 population and the population at risk in northern Finland in 1969

Age group	Uveitis patients	Incidence rate per 100 000 population	Population
0– 9	1	0 9	11[illegible] 604
10–19	12	8[illegible]	13[illegible] [illegible]30
20–29	28	29 7	94 257
30–39	22	29 3	75 101
40–49	27	37 3	72 400
50–59	17	31 3	54 195
60–69	8	20 4	39 206
70+	5	21 4	23 355
Total	120	19 6	613 426

Table II

Incidence rates of uveitis per 100 000 population with regard to sex and age in northern Finland in 1969

Age group	Males with uveitis	Incidence rate per 100 000 males	Females with uveitis	Incidence rate per 100 000 females	Male population	Female population
0– 9	–	–	1	1 7	60 156	57 448
10–19	5	7 1	7	10 5	70 890	66 418
20–29	14	28 1	14	31 5	49 763	44 494
30–39	13	33 2	9	2[illegible] 0	39 135	35 966
40–49	15	40 8	12	33 6	36 741	35 649
50–59	8	30 7	9	32 0	26 037	28 163
60–69	2	11 4	[illegible]	2[illegible] 7	17 555	21 651
70+	3	31 3	2	14 3	9423	13 932
Total	60	19 3	60	19 7	309 705	303 721

Table III

Incidence rates of uveitis per 100 000 population with regard to type of uveitis and age group in northern Finland in 1969

Age group	Patients with anterior uveitis	Incidence rate per 100 000 population	Patients with posterior uveitis	Incidence rate per 100 000 population	Patients with generalized uveitis	Incidence rate per 100 000 population
0– 9	1	0.8	–	–	–	–
10–19	9	6.5	1	0.7	–	1.4
20–29	23	24.4	4	4.2	1	1.1
30–39	20	26.6	2	2.7	–	–
40–49	24	33.1	3	4.1	–	–
50–59	15	27.6	–	–	2	3.3
60–69	8	20.4	–	–	–	–
70+	5	21.4	–	–	–	–
Total	105	17.1	10	1.6	5	0.8

tion period of 6 years The distribution of types of uveitis in age groups and respective incidence rates per 100 000 population are indicated in Table III Four males and six females had posterior uveitis while one male and four females had generalized uveitis

55 males and 50 females had anterior uveitis and the incidence rates for anterior uveitis per 100 000 population were 17 8 in males and 16 5 in females No statistically significant differences were found in the incidence rates for anterior uveitis with regard to age between males and females

20 % of uveitis patients depended on agriculture while in the 1970 census the respective rate was 26 %. Table IV shows the percentage distribution of 120 uveitis patients into outdoor occupations and occupations with risks for eye injuries Respective general distribution of residents of northern Finland in the 1970 census is also shown

The monthly onset of new cases with uveitis was even during 1969 in northern Finland There were no statistically significant differences between the months of admission

In this material of the 120 new uveitis cases 97 (81 %) were of unknown origin The aetiology could be defined in 23 (19 %) The aetiology of cases

Table II

The percentage distribution of 190 new uveitis patients in 1969 divided into outdoor occupations and occupations with risks for eye injuries and compared with the respective 1970 census figures of the whole population of northern Finland

	Manual labour in the open air	All occupations with manual labour
Uveitis patients (190)	55 %	52 %
1970 census (598 316)	44 %	58 %

Table I

Aetiological factors in anterior and posterior uveitis of new patients with uveitis in northern Finland in 1969

Aetiology	Anterior uveitis	Posterior uveitis
Undetermined	91	5
Toxoplasmosis	–	4
Streptococcal	4	–
Rheumatoid	4	
Tuberculosis	1	1
Sarcoidosis	1	–
Leptospirosis	–	–
Staphylococcal	1	
Meningococcal	1	–
Varicella zoster	1	–
Herpes simplex	1	
Total	105	10

with anterior and posterior uveitis is shown in Table V Five patients had generalized uveitis and the aetiology was toxoplasmosis in three leptospirosis in one and undetermined in one

Seven patients had ocular toxoplasmosis and five of them lived in towns and two in the countryside

Discussion

In a 10 year retrospective survey in Rochester, USA the incidence rate of uveitis was 17 per 100 000 population (Darrell et al 1962). In the present study it was 19.6 per 100 000 population and in spite of genetic, climatological and geographical differences the incidence rates showed equal trends also in different age groups. Darrell et al (1962) found no statistically significant difference with regard to sex which agreed with the results of this study (Table II).

The low incidence of uveitis in the age groups 0–9 years and 10–19 years agreed with earlier accounts according to which uveitis is uncommon in children (Perkins 1966). The onset of uveitis was predominantly in the fertile age, for the incidence rate began to rise in adolescence, was high in young and middle aged adults and fell again in old age (Table II).

In northern Norway Bergaust (1962) found that fishermen were very prone to uveitis but craftsmen and industrial or agricultural workers were not. In the present material males had more outdoor work than females but still the sex distribution was equal. Table IV shows that the general character of daily work was not important in the onset of uveitis.

The summer is warm and extremely light and the winter cold and dark in this subarctic district but admissions of patients did not correlate with seasonal changes. Contrary to these results Bergaust (1962) found that symptoms of uveitis appeared more often in the autumn than in the spring and summer.

The cold climate in northern countries might decrease the prevalence of toxoplasmosis (Saari et al 1975). In this study five patients with ocular toxoplasmosis lived in towns and only two patients lived in the countryside though two thirds of the population at risk had rural residence. Greater patient material would be needed in order to determine whether the incidence of toxoplasmosis in a cold climate is higher in an urban than in a rural population.

The incidence rate of anterior uveitis was in the present material 17.1 per 100 000 population. In Rochester, USA (Darrell et al 1962) it was 12 per 100 000 population, whereas the incidence rates of posterior and generalized uveitis were twice the respective rates in northern Finland. In Oulu Saari et al (1975) found that 83.8 % of all their uveitis cases were anterior and in this study uveitis was anterior in 88 %. In the study of Perkins (1968) uveitis was anterior in 63 % in London and in 37.3 % in Baltimore, USA.

In this study uveitis was mostly acute, anterior and of unknown aetiology although the incidence of rheumatoid uveitis might be higher than 4 (Table V).

because X rays of sacroiliac joints were not performed in the hospitals of northern Finland in 1969 unless patients had lower back symptoms

The histocompatibility antigen B27 has been found in a high proportion of patients with acute anterior uveitis as compared with controls (Brewerton et al 1973 1974 Ehlers et al 1974 Mapstone & Woodrow 1975) An association between a certain HLA type and a given disease implies that there is a genetic component in the aetiology of the disease (McDevitt & Bodmer 1974 Aho et al 1974)

In a random Finnish population of 326 persons HLA B27 was found in 14 % (Tiilikainen et al 1972) In England the frequency of HLA B27 was 8 2 % in a control material of 233 persons (Mapstone & Woodrow 1975) and in the United States Schlosstein et al (1973) found HLA B27 in 8 % of 906 normal controls In 10 studies from Europe and the United States reviewed by McDevitt & Bodmer (1974) the frequency of HLA B27 was 6–8 % in control populations

The high incidence of acute anterior uveitis in this study was in accordance with the high frequency of HLA B27 among Finns The aetiology of anterior uveitis was mostly undetermined and the onset of uveitis did not correlate with the environmental factors examined in the present material These results lend further support to the idea that predisposing genetic factors are implicated in the onset of acute anterior uveitis

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References

Aho K Ahvonen P Alkio P Lassus A Sairanen E Sievers K & Tiilikainen A (1975) HL A27 in reactive arthritis following infection *Ann rheum Dis* 34 Suppl 29–30

Bergaust B (1969) Uveitis As seen in material from a hospital in the Arctic Circle *Acta ophthal (Kbh)* 40 443–451

Brewerton D A Caffrey M Nicholls A Walters D & James D C O (1973) Acute anterior uveitis and HL A27 *Lancet* ° 994–996
Brewerton D A Caffrey M Nicholls A Walters D & James D C O (1974) Acute anterior uveitis and HL A27 *Lancet 1* 464
Central Statistical Office of Finland (19/3) Corrected population statistics 31 1° 1969 Helsinki
Darrell R W Wagener H P & Kurland L T (196°) Epidemiology of uveitis *Arch Ophthal (Chicago) 68* 502–513
Ehlers N Kissmeyer Nielsen F Kjerbye K E & Lamm L U (1974) HL A°7 in acute and chronic uveitis *Lancet 1* 99
Mapstone R & Woodrow J C (1975) HL A27 and acute anterior uveitis *Brit J Ophthal 59* 270–275
McDevitt H O & Bodmer W F (1974) HL A immune response genes and disease *Lancet 22* 1269–1274
Perkins E S (1961) *Uveitis and toxoplasmosis* pp 6–8 Churchill London
Perkins E S (1966) Pattern of uveitis in children *Brit J Ophthal 50* 169–185
Perkins E S (1968) Uveitis survey at the Institute of Ophthalmology London In Aronson S B Gamble C N Goodner E K and O Connor G R Eds *Clinical methods in uveitis* pp 58–65 Mosby St Louis
Population census 1970 In *Official Statistics of Finland VI C 104* (1973) pp °00–°01 Helsinki
Saari M Miettinen R & Alanko H (1975) Uveitis Report of a 10 year survey in Northern Finland *Canad J Ophthal 10* 356–360
Schlosstein L Terasaki P I Bluestone R & Pearson C M (1973) High association of an HL A antigen W27 with ankylosing spondylitis *New Engl J Med* °8° 704–706
Suomi kasikirja (1968) pp 106–113 880 10°3 1084 Otava Helsinki
Tiilikainen A Eriksson A W MacQueen J M & Amos D B (19/?) The HL A system in Scolt Lapp population In Dausset J and Colombani J Ed *Histocompatibility testing* pp 85–92 Munksgaard Copenhagen

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EFFECTS OF REPEATED SMOKING ON DARK ADAPTATION

BY

BERIT CALISSENDORFF

The influence of cigarette smoking on adaptation of the eye to the dark has been studied in 12 subjects with the aid of an automatic adaptometer After repeated smoking a slight but significant impairment of dark adaptation in the mesopic range was noticed

Key words dark adaptation – nicotine – smoking – tobacco

The effect of smoking on visual functions especially dark adaptation is a con troversial subject Many experimental studies using different techniques have been performed to find out whether or not a connection exists between smoking and dark vision The results have been somewhat contradictory While McFarland et al (1944) reported that the smoking of three cigarettes was enough to increase the carboxyhaemoglobin in the blood to such a level as to affect dark vision Sheard (1946) attributed the impaired dark vision in a smoking experiment to the amount of nicotine However according to Johans son et al (1965) dark vision and perception in dimlight were not appreciably influenced by tobacco smoking Other studies (Troemel 1951 Bohne 1962) even showed improved dark vision after smoking

Studies on carbon monoxide as a potential cause of impaired dark vision have since been carried out Halperin et al (1959) and McFarland (1970) showed that increased carboxyhaemoglobin in blood had a depressive effect on visual function As for nicotine no certain direct effects on dark adaptation

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have been reported but it is known that nicotine influences visual functions in many ways Thus small doses of nicotine increased the b wave of the electro retinogram (ERG) in guinea pig while large doses resulted in a decrease of the b wave (Muller Limmroth & Hieronymus 1962) Nicotine also has a circulatory effect on the eye increasing the choroidal blood volume (Bettman et al 1958) Furthermore nicotine in small doses has a stimulating and later a depressing effect on the nervous system an effect that probably also influences the eye

The effects of smoking are more complicated and contradictory than those of pure nicotine or carbon monoxide While Himmelmann & Rosemann (1938) and Junemann & Damaske (1968) have reported that tobacco smoking reduced the b wave of the human ERG Straub & Winkelmann (1959) found an increase of the b wave Smoking has also been shown to have a varying effect on human choroidal volume sometimes causing a vasoconstriction and sometimes a vaso dilatation (Bettman et al 1958)

These conflicting results made it of interest to study the effects of repeated tobacco smoking on dark adaptation as the different effects found might be a question of dose and time Furthermore an automatic adaptometer with time limited testlight introduces a time component in the procedure a factor that might be of importance for the registration of dark adaptation

Methods and Material

An automatic adaptometer constructed by Krakau and Öhman was used (for detailed descriptions see T Krakau & R Öhman 1966)

The advantage of this adaptometer is that the testlight is time limited thus increasing the demands upon the performance of the subject Furthermore the automatic recording eliminates the possibility of errors on the part of the investigator

Twelve subjects with healthy eyes and ranging from 20–50 years of age were tested Refractive errors were corrected with glasses Ten of the examined persons were moderate smokers (5–10 cigarettes/day) and two were occasional smokers The registration of the dark adaptation was made in two sequences at an interval of one or two days One series was a control without smoking and the other included the smoking of two cigarettes As far as possible the two examinations were performed at the same time of the day The subjects were instructed not to smoke or drink coffee two hours prior to the examination All subjects had received instructions as to the operation of the adaptometer and were accustomed to the testing procedure

The subjects were kept in faint light for 20 min and were then light adapted for 5 min in the pre adaptation light of the apparatus (illumination about 5000 lux) Immediately following this procedure the dark adaptation was re gistered in complete darkness for 25 min After this registration the faint light was turned on and the subject had to sit in the dimlight for 5 min, a period corresponding to the time it would take to smoke a cigarette Then the pre adapting light was turned on for a further 5 min followed by a repeated re gistration of the dark adaptation The same procedure i e sitting in the dim light for a while followed by 5 min of pre adaptation light and then a re gistration of the dark adaptation was repeated for the third time At another time the some sequence of three registrations of the dark adaptation was executed The only differences from the preceding examination was that this time the subjects smoked a cigarette in each break as they sat in the faint light Thus the timing and light conditions were identical in the two separate series of registrations In four of the examinationes the sequence including the cigarette smoking took place prior to the control series

In an additional experiment two subjects were allowed to reach a level of adaptation to the dark where no further improvement could be registered i e after 45 min They were then allowed to smoke in two rounds and after each round the level of adaptation was registered over a period of 25 min They remained in a dark experimental room for the whole duration of the ex periment

Results

The effect of cigarette smoking upon dark adaptation was studied in 12 sub jects Two series of experiments each comprising three registrations were performed One series (A) (Fig 1) served as a control and the other series (B) (Fig 2) included the smoking of two cigarettes by the subjects

The results of these two examinations are illustrated in the figures The relative light intensity is plotted on the ordinate and the time in minutes on the abscissa Each curve represents the mean value for all 12 subjects during the respective experiments

Comparing each registration from series A with respective registration from series B no statistically significant difference was found as the individual variations were quite large and the number of tested subjects small Further more there was a variation in performance of one and the same subject from one experimental occasion to the other In both series there is an improvement of dark adaptation when the first and second registrations are compared In

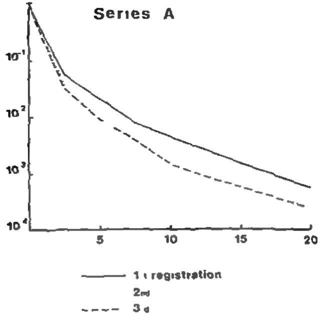

Fig 1
The average dark adaptation curves of three consecutive registrations
In this series no smoking was allowed

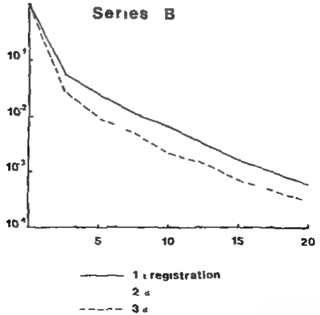

Fig 2
The average dark adaptation curves of three consecutive registrations
Before the 2nd and 3rd registration the subjects had smoked one cigarette

series A there is a further improvement in the final third registration However in series B the third registration although improved when compared with the first shows an impaired course compared with the second registration Thus a noticeable difference is found if the relationship between the registrations 2 and 3 within the respective series is compared It was a consistent finding for all the subjects in the series involving smoking (B) that the third registration showed an impaired course compared to the preceding registration This is in contrast to the control series where at the time of the third registration an additional moderate improvement of the dark adaptation was observed in all the subjects

At the statistical treatment of the data a two sample *t* test was used The difference between the third and the first registration during the respective experimental series have been calculated for each individual On an average this deviation i e improvement of dark adaptation is found to be greater in series A when the subjects did not smoke than in series B when they smoked The difference between the calculated deviations between the first and third registration of series A and series B was subsequently calculated (difference a–b Table 1) This difference shows that the dark adaptation performance

Table 1

Dark adaptation Differences between control series and series involving tobacco smoking

Time of registration	2.5	5.0	7.5	10.0	12.5	15.0	[illegible]0.0	Min after pre adaptation
a Mean difference between 1st and 3rd registration in control series (A)	6.16	9.33	9.33	9.4[illegible]	8.00	8.00	5.90	scale units of log relative intensity
b Mean difference between 1st and 3rd registration in series (B) involving tobacco smoking	2.00	3.[illegible]5	3.25	4.58	4.66	4.66	5.2[illegible]	
Difference a–b	4.16	5.58	6.08	4.66	3.33	3.33	0.63	
SD (x)	4.36	6.20	6.92	[illegible]96	3.74	5.08	5.69	
P	<0.01	<0.01	<0.02	<0.001	<0.0[illegible]	<0.05	<0.70	

after smoking is deteriorated compared with the control series The difference is most notable during the first 10 min of registration and as the course of adaptation continues the differences level off more and more and after 20 min they are no longer significant

By making the experimental conditions as identical as possible and by comparing the differences between the first and the last registration in each series when making the statistical calculations it has been intended to eliminate the variations in the initial adaptation condition of the subject as well as the eventual variations associated with individual sensitivity

In order to study if the maximum effect reached after 10 min was due to a time factor additional experiments were made Having reached a constant level of registration after 40 min dark adaptation two subjects were at two different intervals allowed to smoke one cigarette After each smoking procedure which was performed in darkness with the subject blind folded the level of adaptation was registered for 15 min No significant impairment of the final level of dark adaptation could be noticed

Discussion

An experiment involving two series of three consecutive registrations of adaptation to the dark in which the one series involved cigarette smoking has shown an impairment in the course of adaptation in smoking subjects This impairment first became apparent after repeated smoking and the degree of influence varied considerably from one individual to another

The complicated pharmacology of tobacco smoke gives rise to a highly complex mechanism of action bringing about effects which many times act in opposition to each other Concerning the question of adaptation to the dark carbon monoxide and nicotine are the components in cigarette smoke expected to be of greatest importance A negative effect of carbon monoxide upon light sensitivity and dark adaptation has been demonstrated by among others McFarland (1970) and McFarland et al (1944 1959) However an increased concentration of carbon monoxide in the blood cannot be the sole explanation for the delayed effect on dark adaptation observed in this study Nicotine possibly in combination with carbon monoxide is likely to play a major role in this connection The negative effects of carbon monoxide could be that of hypoxemia (McFarland 1970) while the effect of nicotine is unclear as this substance has both direct neuronal effects and indirect influences i e circulatory effects (Goodman & Gilman 1975) Furthermore one of the properties of nicotine is that it initially has a stimulating effect and later an inhibitory

effect on certain parts of the nervous system Hence it might be assumed that the initially generally stimulating effect of nicotine counterbalances its eventual negative effects as well as those of carbon monoxide on vision in the dark Such a relationship could explain why no significant differences in performance in the dark were seen after the smoking of 1 cigarette only the inhibitory effect first appearing after repeated smoking when the influence of the initially stimulating factors has lessened An individual sensitivity to such stimulator and/or inhibitory effects could also explain the large individual differences in performance after smoking

The steady improvement of the result as observed in the control series (A) could be an effect of learning This also applies for the improvement seen in series B Another contributing cause could be that the subjects were not sufficiently dark adapted during the first registration despite the fact that they spent about 20 min in dark surroundings prior to the experiment

The range in the dark adaptation process which is most affected by smoking is the mesopic i e the intermediate stage in which the activities of cones and rods overlap The observed impairment is generally not great enough as to be of any practical importance However in individuals especially sensitive to the depressing effects of smoking or with impaired dark vision a noticeable effect in practical terms cannot be excluded Furthermore under circumstances with extreme demands of good adaptation a lowering of the result of individual performance can also be of importance

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References

Bettman J W Fellows V & Chao P (1958) The effect of cigarette smoking on the intraocular circulation *Arch Ophthal (Chicago) 59* 431–433

Bohne G (1967) Der Einfluss des Rauchens auf spezielle fur den Kraftfahrer wichtige Sinnesleistungen des Auges *Klin Mbl Augenheilk Bd 140* 1 –729

Goodman L S & Gilman A (1975) *The Pharmacological Bases of Therapeutics* Mac Millan Publishing Co Inc New York

Halperin M H et al (1959) The time course of the effects of carbon monoxide on visual thresholds *J Physiol (Lond) 146* 583–593

Himmelmann W & Rosemann H U (1933) Über die Wirkung des Nikotins auf das Aktionspotential der Netzhaut *Z Biol 99* 147–15

Johansson G & Jansson G (1964) Smoking and night driving *Scand J Psychol 5* 124–128

Junemann G & Damaske E (1968) Der Einfluss des Rauchens auf das menschliches Elektroretinogramm (ERG) (1968) *Munch med Wschr 10* 586–590

Krakau T & Öhman R (1966) An automatic adaptometer *Forsvarsmedicin 4* 184–189

McFarland R A (1970) The effects of exposure to small quantities of carbon monoxide on vision *Ann N Y Acad Sci 174* 301–312

McFarland R A et al (1944) The effects of carbon monoxide and altitude on visual thresholds *J Aviat Med 15* 381–394

McFarland R A et al (1959) The time course effects of carbon monoxide on visual thresholds *J Physiol (Lond) 146* 583–593

Muller Limmroth W & Hieronymus J (1962) Die Wirkung des Nikotins auf das Elektroretinogramm *Arch int Pharmacodyn 135* 68–90

Sheard C (1946) The effects of smoking on the dark adaptation of rods and cones *Fed Proc 5* 94

Straub W & Winkelmann J (1959) Versuche uber die Beeinflussung der B Wellen amplitude des menschlichen Elektroretinogramm *Acta Fac pharm Brun Bratisl 4* 179–184

Troemel R G et al (1951) Dark adaptation as a function of caffeine and nicotine administration *Proc S D Acad Sci 30* 79–84

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ASPECTS ON THE TREATMENT OF GLIOMAS OF THE ANTERIOR VISUAL PATHWAY

BY

H BYNKE E KÅGSTRÖM* and K TJERNSTRÖM

Partial excision of the glioma of the anterior visual pathway seemed to have no effect on the vision in 7 patients and had a negative effect in 2 These results support the opinion that no excision should be made in such tumours However the course of the disease in one exceptional patient raises doubts about the general validity of this rule In this case the postulated chiasmal glioma proved to be an exophytic glioma arising in one intracranial optic nerve and compressing the other Excision of the exophytic portion caused rapid and considerable improvement of vision in both eyes Direct visualization by craniotomy was needed to separate this mode of growth from the common intrinsic growth of such tumours

Key words chiasmal glioma – optic nerve glioma – visual function – excision – irradiation

The treatment of gliomas of the anterior visual pathway is still controversial Although it has been known for a long time that these tumours are relatively benign and grow very slowly they have been treated with total or partial excision often resulting in loss of vision In 1969 Hoyt & Baghdassarian presented convincing evidence in favour of a conservative approach They stated that these gliomas are benign hamartomas which tend to grow and cause symptoms in childhood and then remain static

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Table I

Eleven cases of glioma of the anterior visual pathway

Case Sex Years	Preoperative clinical findings	Pertinent neuro radiological findings	Treatment	Postoperative follow up	Course* L E	Course* R E
MR male 10	0 7 L E 0 4 R E homonymous hemianopsia esotropia R E bilateral papilloedema headaches and vomiting	suprasellar tumour with calcification Craniopharyngioma	partial excision + shunting + irradiation	10 years 9 months	→	→
BJ female 2?	1 0 L E 1 0 R E homonymous hemianopsia pale discs menarche at 9 years Recklinghausen s disease	enlarged right optic foramen J shaped sella shortened dorsum Chiasmal glioma	craniotomy without biopsy	7 years 6 months	→	→
TN male 6	finger counting L E 5/7 5 R E bitemporal hemianopsia pendular nystagmus pale discs enlarged head vomiting	shortened dorsum undefined suprasellar tumour	partial excision + irradiation	9 years	0	↓
I B female 1	0 4 L E finger counting R E bitemporal hemianopsia pale discs Recklinghausen s disease	enlarged left optic foramen Chiasmal glioma	partial excision	10 years 6 months	←	0
AJ female 6	5/7 5 L E 5/7 5 R E bitemporal hemianopsia irregular nystagmus exotropia L E bilateral papilloedema retardation ataxia and left hemiparesis	J shaped sella Chiasmal glioma or craniopharyngioma	partial excision + shunting + irradiation	5 years	■	0

LL male 18	0 5 L E hand movement R E homonymous hemianopsia pale discs diabetes insipidus	J shaped sella Chiasmal glioma	partial excision + irradiation	11 months (deceased)	0	0
LA female 7	1 0 L E finger counting R E bitemporal hemianopsia esotropia and pale disc R E	enlarged right optic foramen J shaped sella Chiasmal glioma	partial excision + irradiation	2 years 11 months	0	→
JS male 13	0 8 L E finger counting R E homonymous hemianopsia pale discs	J shaped sella Chiasmal glioma or craniopharyngioma	partial excision + irradiation	4 years 6 months	←	←
KH female 13	0 5 L L 0 6 R E bitemporal hemianopsia pale discs	J shaped sella shortened dorsum Chiasmal glioma	partial excision + irradiation	3 years	←	←
JT male 4/12	proptosis elevation paresis and papilloedema L E normal pupils	enlarged optic foramen both sides J shaped sella thickened optic nerves left orbital tumour Chiasmal glioma	craniotomy + biopsy + orbital unroofing + irradiation	2 years 6 months	↓	20
BS male 18	finger counting L E 0 1 R L non hemianopic defects normal discs	enlarged right optic foramen J shaped sella Chiasmal glioma	partial excision	4 years 11 months	↑	↑

* 0 indicates no change of visual function → delayed deterioration ← delayed improvement ↓ rapid deterioration ↑ rapid improvement

In this discussion gliomas involving the chiasm should be distinguished from those confined to the optic nerve Already in 1923 Martin & Cushing proposed that surgery was not indicated in chiasmal glioma This is today generally accepted with the exception that intracranial hypertension may require shunting procedures As regards gliomas confined to the optic nerve some researchers e g McCarty et al (1970) and Lloyd (1973) suggested active surgery even with resulting loss of vision This is contrary to the conservative approach advocated by Hoyt & Baghdassarian (1969) that no excision should be performed unless the eye is blind and proptotic and that the diagnosis should be made by neuro radiology only

The conservative statement has principally been supported by Wong & Lubow (1972) and Miller et al (1974) but these authors and Lindenberg et al (1973) recommended craniotomy with biopsy to confirm the neuro radiological diagnosis The pitfalls of this diagnosis have been demonstrated by among others Block et al (1973) who reported a case of craniopharyngioma with enlargement of the optic canal a sign usually indicating optic glioma

Another controversial point concerns the value of irradiation While e g Taveras et al (1956) found irradiation effective Glaser et al (1971) showed that it is of no use as far as vision is concerned

We have seen a patient whose vision improved considerably following partial excision of an exophytic optic glioma It was chiefly this case which made us present our material and discuss this subject

Material and Methods

During the past decade 17 patients with glioma of the anterior visual pathway have been examined at the Unit of Neuro Ophthalmology Lund Fifteen of them have been operated upon in the Department of Neurosurgery Lund and 2 in other neurosurgical clinics Out of these 17 patients 11 constitute the basis of the present study

Five patients were infants whose visual function could not be tested in any detail Their suprasellar tumours were huge and they were operated upon on vital indications From an ophthalmological point of view these 5 cases are less interesting and have been excluded from the present material A sixth patient a mentally retarded nine year old boy with Recklinghausen s disease has been excluded since he was followed for only two months and did not cooperate with perimetry

The remaining 11 cases are demonstrated in Table I At the time of surgery between 1965 and 1973 they were between 4 months and 22 years old (mean 12 years) The glioma originated in the chiasm and adjacent visual pathway in 9 cases and was confined to the intracranial optic nerve in one case (BS) The site of origin was uncertain in one case (AJ)

The postoperative follow up periods ranged from 11 months to 10 years 9 months (mean 6 years 2 months) Repeated neuro ophthalmological examinations if possible including quantitative kinetic perimetry with Goldmann s instrument were performed before and after treatment The majority of these examinations were made at this hospital

Preoperative findings

The symptoms and signs were mainly ophthalmic (Table I) Nine out of the 11 patients had reduced visual acuity Five had bitemporal hemianopsia 4 homonymous hemianopsia and 1 non hemianopic field defects Seven patients had primary optic atrophy 2 bilateral papilloedema and 1 normal discs The youngest patient with unilateral proptosis had papilloedema of that eye and normal pupillary light response Concomitant squint existed in 3 patients and congenital nystagmus in 2

Two patients had cutaneous neurofibromatosis (Recklinghausen s disease) Other extra ocular findings were enlarged head in 1 patient vomiting in 2 endocrine dysfunction in 2 and mental retardation ataxia and hemiparesis in 1 patient

Nine patients had enlarged optic canals and/or J shaped sella The supra sellar tumour was large enough to deform the third ventricle in 10 cases In the youngest patient the suprasellar portion was small and the tumour mainly intraorbital The neuro radiological diagnosis was probable chiasmal glioma in 7 cases chiasmal glioma or craniopharyngioma in 2 and probable cranio pharyngioma in 1 case with suprasellar calcifications In 1 patient the diagnosis of the suprasellar tumour could not be made by neuro radiology

Treatment

Craniotomy with exploration of the chiasm was made in all 11 cases (Table I) The tumour was found to be located in the chiasm as well as in one or both optic nerves in 9 cases In 5 of them it also involved one optic tract In one case (AJ) the tumour grew like a pituitary adenoma attenuating and dis locating both nerves laterally The site of origin could not be ascertained in that case In one single case (BS) the tumour was confined to one intracranial optic nerve but compressed and attenuated the other nerve (see case report)

In one patient with Recklinghausen s disease (BJ) no biopsy was made In the other 10 cases partial excision or biopsy was performed and the diagnosis verified by histology In the infant with unilateral proptosis (JT) exploration of the chiasm was combined with biopsy and unroofing of the orbit Shunting procedures were made in the 2 patients with bilateral papilloedema

Eight patients were given postoperative irradiation as well The doses ranged between 3300 and 5300 rad

Postoperative course

One patient (LL) developed panhypopituitarism and multiple cranial nerve palsies and died 11 months after surgery since his glioma was malignant At

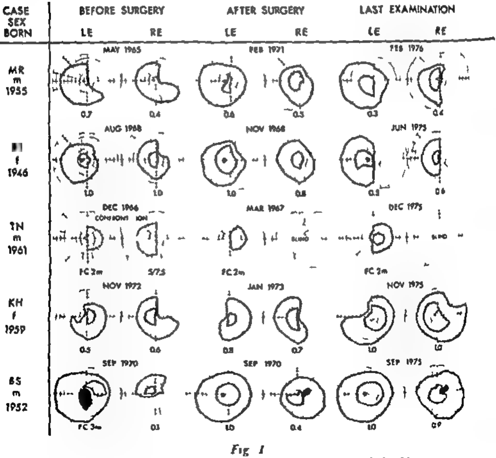

Fig 1
Visual fields and visual acuity on three occasions in 5 of the 11 cases

the time of operation there were no signs indicating malignancy but a few weeks prior to death malignant cells were found in his CSF The other 10 patients are still alive In 8 of them the general condition is good but 2 patients (BJ and AJ) have developed progressive ataxia and one (AJ) progressive mental deterioration

The course as regards visual function appears from Table I and Fig 1 In 2 patients (LL and AJ) vision has been stable for eleven months and eight years respectively In 3 patients (MR BJ and LA) there has been a gradual loss of vision in one or both eyes over periods ranging from almost three to almost eleven years One of them was BJ in whom neither biopsy nor irradiation was performed In another 3 patients (LB JS and KH) a gradual improvement has taken place in one or both eyes over periods ranging from three to more than ten years Two of them (JS and KH) were irradiated as well In KH repeated postoperative pneumoencephalograms disclosed a gradual decrease of the remaining glioma In 2 patients (TK and JT) one eye was found to be blind at the first postoperative examination One of them was the infant with unilateral proptosis (JT) who no longer had any direct pupillary light response in that eye

In one exceptional case (BS) vision was found to be much improved in both eyes at the first postoperative examination and a further improvement occurred during the subsequent five years This patient deserves a detailed report

Case Report

BS a man aged 18 years No family history of visual impairment or neurofibromatosis One healthy brother and two healthy sisters His somatic and mental development had been normal and except for a period of asthma as a child he had previously been mainly healthy His vision was said to have been normal when tested at a medical examination at the age of 14 years

On *May 5 1970* an eye examination was performed after his right eye had been hit by a piece of bakelite The visual acuity was finger counting at 1 m R E and normal L E A temporal defect was found in the right field the left being normal Both discs were normal X ray examination of the skull and a general neurological examination revealed nothing abnormal In the *middle of August* he noticed visual impairment also in his left eye A few weeks later bilateral non hemianopic field defects were found On *Sep 1* a pneumoencephalography showed that the anterior part of the third ventricle was dislocated by a suprasellar tumour

He was referred to the Department of Neurosurgery Lund On *Sep 29* the visual acuity was 0 1 R E and finger counting at 3 m L E Only the upper nasal quadrant was spared in the right field and there was an absolute central scotoma in the left

(Fig 1) The pupillary light reflexes were sluggish The temporal half of the right optic disc was slightly pale and excavated but this was interpreted to be within normal limits A general neurological examinations was normal and there was no endocrine dysfunction X rays of the skull with tomography showed enlargement of the right optic canal and a J shaped sella Bilateral carotid angiography confirmed the existence of a suprasellar tumour The neuro radiological diagnosis was probable chiasmal glioma

On *Sep 23 1960 the chiasmal region was explored through a right frontotemporal* craniotomy The tumour seemed to infiltrate the right optic nerve which was broadened flattened and attenuated from the optic canal to the chiasm (Fig 2) The latter structure seemed to be free of infiltration. From the medial and caudal side of the right optic nerve a rounded solid tumour extended between the optic nerves. This exophytic portion compressed and dislocated the left optic nerve which was attenuated This portion was excised from its origin in the right nerve The site of origin measured only about 3 x 3 mm and was located at the medial caudal and posterior aspect of the right optic nerve A histological examination showed an astrocytic glioma of the characteristic type (Fig 3)

At the first postoperative examination on *Sep 29* the visual acuity was 0 4 R E and 1 0 L E The right field was considerably enlarged and the left was full (Fig 1) Over the subsequent years there was a gradual further improvement of vision of the right eye At the last examination on *Sep 1 1975* visual acuity was 0 9 R E and still normal L E The right field was defective mainly in its upper quadrants and the blind spot considerably enlarged The left field was still normal The right disc was extensively pale and excavated the left normal

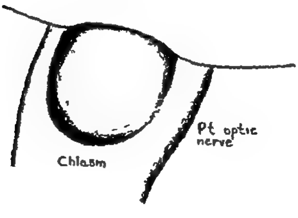

Fig 2
Exophytic optic nerve glioma of BS at surgical exploration

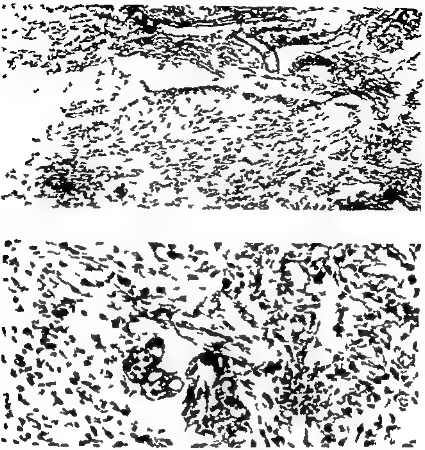

Fig 3

Surgical specimens of optic glioma of BS showing tumour consisting of astrocytic tumour cells of a pilocytic elongated shape forming fascicles (a) or more loose textured tumour tissue (b) There is little or no vascular proliferation and no necrosis Haematoxylin and eosin a = x 100 b = x 160

Discussion

The neuro radiological diagnosis was probable chiasmal glioma in 7 patients but craniopharyngioma could not be excluded in the other 4 cases Craniopharyngioma seemed very probable in the patient with suprasellar calcifications Diagnostic craniotomy was felt to be necessary in all the 11 cases This agrees with the opinion of Wong & Lubow (1972) Lindenberg et al (1973) and Miller et al (1974) who thought it unwise to rely upon clinical judge

ments and neuro radiological findings alone With an improved neuro radio logical technique e g the introduction of computerized tomography craniotomy may be expected to be avoidable in a number of cases but probably not in all

It is beyond the scope of this article to evaluate the effect of treatment on the extra ocular disturbances It should only be mentioned that shunting procedures were required to relieve the intracranial pressure in 2 patients with bilateral papilloedema and other neurological signs which is also consistent with general opinion

During the postoperative follow up period the visual function was unchanged in 2 patients gradually decreased in 3 and gradually increased in 3 patients (Table I Fig 1) Six out of these 8 patients were treated with partial excision and irradiation but one whose vision gradually decreased was not treated at all and another one whose vision gradually increased was treated by surgery only It is difficult to evaluate the effect of the treatment in these cases

It should be noted that the visual changes did not appear in direct connection with the treatment Furthermore Tym (1961) and Hoyt & Baghdassarian (1969) have described delayed improvement in the absence of any treatment at all Therefore it is tempting to suggest that the course was spontaneous and not attributable to surgery or irradiation Because there was no obvious positive effect of the latter treatment we are also inclined to agree with Glaser et al (1971) that irradiation is of no value in chiasmal glioma

One of the cases with unchanged visual function was the patient whose glioma proved to be malignant His course differed from that described previously in malignant glioma of the anterior visual pathway (Hoyt et al 1973 Manor et al 1976) where there was progression to blindness within some weeks

Whereas the effect of the treatment was difficult to evaluate in the 8 patients just discussed there can be no doubt that the instantaneous loss of vision in one eye that occurred in 2 patients was caused by the excision This supports the general opinion that no excision should be made in glioma of the chiasm and optic nerve

The most remarkable case in this small series is the patient whose vision improved instantaneously and considerably following surgery This was not a chiasmal glioma but an exophytic glioma originating from the right optic nerve that compressed the left optic nerve Exophytic growth has been mentioned by Martin & Cushing (1923) Taveras et al (1956) and Udvarhelyi et al (1966) but none of them has described visual improvement after sur

gery in such cases Nevertheless this mechanism may explain the successful effect of the excision in the present case

As mentioned the natural history of these gliomas makes it difficult to evaluate the effect of any treatment and it may be objected that even in the exceptional case the improvement was spontaneous and not due to surgery We admit that it might have been partly spontaneous in the right eye which possibly improved already before surgery and improved gradually in the post operative period But we do not believe that the left eye would have become *normal without the excision of the solid tumour portion At all events this* exceptional course raises doubts as to the opinion that conservatism is always the best choice

It must also be emphasized that this mode of growth could be diagnosed only by direct visualization and not by neuro radiology This means that diagnostic craniotomy is indicated not only to confirm or reject the preliminary neuro radiological diagnosis but also to reveal compression by an exophytic glioma

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References

Block M A Goree J A & Jimenez J P (1973) Craniopharyngioma with optic canal enlargement simulating glioma of the optic chiasm *J Neurosurg 39* 523–527
Glaser J S Hoyt W F & Corbett J (1971) Visual morbidity with chiasmal glioma *Arch Ophthal (Chicago) 85* 3–12
Hoyt W F & Baghdassarian S A (1969) Optic glioma of childhood *Brit J Ophthal 53* 79 – 98
Hoyt W F Meshel L G Lessel S Schatz N J & Suckling R D (1973) Malignant optic glioma of adulthood *Brain 96* I 1–13?
Lindenberg R Walsh F B & Sacks J G (1973) In *Neuro ophthalmology of Vision An Atlas* p 120 Lea & Febiger Philadelphia
Lloyd L A (1973) Gliomas of the optic nerve and chiasm in childhood *Trans amer ophthal Soc 71* 488–535
MacCarty C S Boyd A S & Childs D S (1970) Tumors of the optic nerve and optic chiasm *J Neurosurg 33* 439–444

Manor R S Israeli J & Sandbank U (1976) Malignant optic glioma in a 70 year-old patient *Arch Ophthal (Chicago) 94* 1142–1144
Martin P & Cushing H (1923) Primary gliomas of the chiasm and optic nerves in their intracranial portion *Archs Ophthal (N Y) 52* 209–241
Miller N R Iliff W J & Green W R (1974) Evaluation and management of gliomas of the anterior visual pathways *Brain 97* 743–754
Taveras J M Mount L A & Wood E H (1956) The value of radiation therapy in the management of glioma of the optic nerves and chiasm *Radiology 66* 518–525
Tym R (1961) Piloid gliomas of the anterior optic pathways *Brit J Surg 49* 322–331
Udvarhelyi G B Khodadoust A A & Walsh F B (1966) Gliomas of the optic nerve and chiasm in children An unusual series of cases *Clin Neurosurg 13* 204–237
Wong I G & Lubow M (1972) Management of optic glioma of childhood A review of 42 cases In *Neuro ophthalmology Symposium of Univ Miami and Bascom Palmer Eye Inst* Vol VI pp 51–60 C V Mosby St Louis

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ATYPICAL RETINITIS PIGMENTOSA

A Case Report

BY

BERIT CALISSENDORFF

A case of retinal degeneration is reported The case shows the characteristics of retinitis pigmentosa pigmentary changes of the fundus constricted visual fields and non recordable ERG but has a normal dark adaptation The contradictory findings are discussed

Key words retinitis pigmentosa – dark adaptation – fluoresceinangiography

Retinitis pigmentosa is a term commonly used to describe a tapetoretinal dystrophy with a distinct hereditary nature The disorder is characterized by progressive changes in the pigment epithelium and retinal receptors particularly the rods (Kolb & Gouras 1974) Clinically the disease is characterized by an attenuation of the retinal vessels optic atrophy and almost invariably widespread pigmentary changes in the retina associated with night blindness contraction of the visual field and eventual diminution of central vision and absence of the electroretinal responses" (Duke Elder & Dobree 1967) The present paper reports a case which fulfils the above mentioned clinical criteria for retinitis pigmentosa with the exception of a normal dark adaptation

Case Report

This 4? year old woman with a history of visual field diminution was initially examined at an ophthalmological department in 1971 During the previous 10–15 years the patient had observed a tendency to bump into surrounding objects There was no

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Manor R S Israeli J & Sandbank U (1976) Malignant optic glioma in a 70 year-old patient *Arch Ophthal (Chicago) 94* 1142–1144

Martin P & Cushing H (1923) Primary gliomas of the chiasm and optic nerves in their intracranial portion *Archs Ophthal (N Y)* 52 209–241

Miller N R Iliff W J & Green W R (1974) Evaluation and management of gliomas of the anterior visual pathways *Brain 97* 743–754

Taveras J M Mount L A & Wood E H (1956) The value of radiation therapy in the management of glioma of the optic nerves and chiasm *Radiology* 66 518–528

Tym R (1961) Piloid gliomas of the anterior optic pathways *Brit J Surg 49* 322–331

Udvarhelyi G B Khodadoust A A & Walsh F B (1966) Gliomas of the optic nerve and chiasm in children An unusual series of cases *Clin Neurosurg 13* 204–237

Wong I G & Lubow M (1972) Management of optic glioma of childhood A review of 42 cases In *Neuro ophthalmology Symposium of Univ Miami and Bascom Palmer Eye Inst* Vol VI pp 51–60 C V Mosby St Louis

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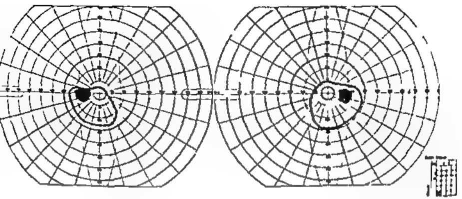


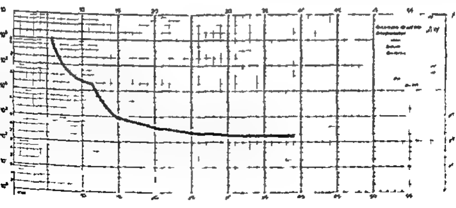
Fig [illegible]

Severely constricted visual fields (Nov 1975)

cence involving the whole fundus except the macular area The hyperfluorescence appeared in the early arterial phase and increased gradually Laboratory data (blood cell count urinanalysis erythrocyte sedimentation rate fasting blood glucose blood urea nitrogen WR) and general medical and neurological examinations were normal

Discussion

Reduced night vision is usually the first symptom noticed by the patient suffering from retinitis pigmentosa In this case the reduced visual fields prompted neurological investigation The suspicion of a tapetoretinal degeneration arose



Fig

[illegible]

at ophthalmoscopic examination ERG confirmed the diagnosis although the normal dark adaptation evoked some consternation

The non recordable ERG indicates a wide spread retinal lesion affecting both the receptors and the neuroretina A large retinal involvement is further indicated by the constricted visual fields and the fluorescein angiography which demonstrated derangement in the pigment epithelium as well It is surprising that such an extensive retinal lesion would fail to affect visual acuity colour vision and particularly dark adaptation

Although the dark adaptation curve is variable in individual cases (Jayle et al 1950 François et al 1956) diminished scotoptic components or mono phasic registrations are usually obtained in cases of retinitis pigmentosa Some features of early reports of retinitis pigmentosa – such as ophthalmic changes with no impairment of dark adaptation – were probably due to syphiles (Jayle et al 1950) No electroretinal examinations were performed in these cases Jacobson (1961) has described two cases similar to that presented in this report His two patients both of them women exhibited the fundus changes constricted visual fields and non recordable ERG s suggestive of retinitis pig mentosa but showed normal dark adaptation Rubino & Ponte (1964) mentioned cases of non recordable or severely impaired ERG in conjunction with normal dark adaptation curves Two of their cases were typical retinitis pigmentosa one was a relative of a patient with genuine retinitis pigmentosa including reduced night vision

The somewhat contradictory findings in this case i e signs of widespread retinal impairment but good visual acuity as well as normal colour and night vision suggest a well preserved function of the rods and cones in the central area This theory is supported by the fluorescein angiography which shows disturbances in the peripheral areas while the macular region is spared Fur thermore the ERG method used in this case gives information on the overall function of the retina the still functional central part of the retina might not be large enough to produce any registrable electrical response As shown by Jacobson et al (1960) and François & De Rouck (1966) among others a retinal lesion must be of a certain size to influence the ERG response Conversely a very small area of functional retina may not be sufficient to elicit any re gistrable electrical potential yet may allow certain visual functions to remain intact Such findings i e decidedly pathological ERG and EOG (electro oculogram) in conjunction with normal dark adaptation were reported in chloroquine retinopathy (Gouras & Gunkel 1963) where small retinal areas remained intact Rubino & Ponte (1964) offered another explanation for pre served night vision in the presence of a "non responsive ERG" They suggested a shunting mechanism similar to the one proposed by Karpe (1945) in which

a normal transmission of visual excitation would continue despite the altered cellular state.

Retinitis pigmentosa is not a uniform abnormality but a generic term used to describe retinal diseases which share certain morphological and psychophysiological properties. Consequently its severity, its demonstrable link with heredity, its occurrence in conjunction with systemic disorders may vary considerably. Although the hereditary factor could not be studied in the reported case, the disorder must be classified as a tapetoretinal dystrophy of the retinitis pigmentosa type, especially as there exists no evidence of influence on the retina by systemic disorders or drugs. It is relevant to mention here the X-chromosome linked type of retinitis pigmentosa, in which the female carriers display considerable variation in severity and symptomatic manifestation of the disease (Warburg 1971, Bird 1975). That this case may in fact represent an X-linked retinitis pigmentosa may derive some support from the two identical cases reported by Jacobson (1961). His two female patients having symptoms of retinitis pigmentosa despite normal dark adaptation had a brother with retinitis pigmentosa whose symptoms included reduced night vision. However, irrespective of hereditary origin the discrepancy between findings and function in the reported case is remarkable.

References

Bird A C (1975) X-linked retinitis pigmentosa. *Brit J Ophthal* 9 1 –199

Duke-Elder S & Dobree J H (196) Diseases of the retina. In *System of Ophthalmology* Vol X Chapter V p 5 . Ed Sir Duke-Elder

François J, Verriest G & De Rouck A (1956) Les fonctions visuelles dans les dégénérescences tapeto-rétiniennes. *Bibl ophthal* 43

François J & De Rouck A (1966) *Behaviour of ERG and EOG in localized destruction by photocoagulation*. In *Clinical electroretinography*. Proceedings of the Third ISCERG Symposium Oct 1964 p 191–20[illegible]. Ed H M Burian and J H Jacobson. Pergamon Press, Oxford

Gouras P & Gunkel R D (1963) EOG in chloroquine and other retinopathies. *Arch Ophthal (Chicago)* 70 629–639

Jacobson J H (1961) *Clinical Electroretinography* p 102. Ed D J Lyle. Charles C. Thomas, Springfield, Illinois

Jacobson J H, Najac H T, Stephens G, Kara G [illegible] & Gestring C F (1960) The role of the macula in the electroretinogram of monkey and man. *Amer J Ophthal* 50 889–900

Jayle G E, *Benoit P H, Blet G, Berard P V & Ourgaud A G (1970) Retinites* Pigmentaires. In *La vision nocturne et ses trouble* p 608–63 . Masson, Paris

Karpe G (1945) The basis of clinical electroretinography. *Acta ophthal (Kbh) Suppl* XXIV

Karpe G (1948) Apparatus and method for clinical recording of the electroretinogram *Docum ophthal (Den Haag)* 2 268–276

Kolb H & Gouras P (1974) Electron microscopic observations of human retinitis pigmentosa dominantly inherited *Invest Ophthal* 13 487–498

Rubino A & Ponte F (1964) Clinical and physiological evaluation of the relationship between dark adaptation and electroretinogram In *Clinical Electroretinography* p 307–310 Ed H M Burian and J H Jacobson Pergamon Press Oxford

Warburg M (1971) Random inactivities of the X chromosome in intermediate X linked retinitis pigmentosa two hypotheses *Trans ophthal Soc U K* 91 553–560

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ULTRASONIC FINDINGS IN THE VITREOUS BODY IN PATIENTS WITH ACUTE ANTERIOR UVEITIS

BY

ARVO OKSALA

The vitreous body of both the healthy and the affected eyes of 25 patients suffering from unilateral acute anterior uveitis was examined by ultrasound and the results were compared with the optical observations made on the affected eye. In 14 eyes the optical examination of the vitreous body was impossible either due to exudation in the anterior chamber or to posterior synechias of the iris or to cataract. In 1[illegible] eyes the vitreous body was acoustically highly inhomogeneous, in three eyes slightly inhomogeneous and in five eyes no acoustic changes due to exudation were found. In cases of acute anterior uveitis ultrasound examination often provides more information than optical examination by slit lamp. Ultrasound can also be useful in the treatment and follow up of the disease.

Key words ultrasonography – ultrasound diagnosis – vitreous body – acute anterior uveitis

Until now there has been little ultrasonic study of the exudation in the vitreous body in acute anterior uveitis. In the first years of ultrasound diagnostics however it had been observed that exudation of the vitreous body in uveitis reflects low echoes (Baum & Greenwood 1958, Oksala 1958, 1959, 1960). Ultrasonic examination was even at that time considered very important in cases where the condition of the vitreous body could not be examined optically due to the opacity of the cornea and the lens (Oksala 1958).

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The ultrasonic examination of vitreous exudation has shown that optically compact but very fine grained exudation which does not form inflammatory cell clusters or other distinct acoustic boundary surfaces is not necessarily detected by ultrasound (Oksala 1969 1974) In acute and chronic uveitis an A scan examination shows the exudation in the form of low and moving echoes which come up more clearly if the inflammation forms membranes in the vitreous body (Bellone & Gallenga 1971) It may be difficult to distinquish between the echograms of the exudation and of blood coagulation but exudation more often takes the form of conglomerations and the amplitudes of its echoes vary more than in the case of haemorrhage (Baum et al 1975)

In the present work the clinical importance of the ultrasound examination of the vitreous body in patients suffering from acute anterior uveitis has been studied in particular by means of a comparison of the optical and ultrasound examination of the vitreous body

Material and Methods

The ultrasonic examination of the vitreous body was performed on 25 consecutive patients with severe acute anterior uveitis whose other eye had always been normal The chief approach was to compare observations made on the vitreous body by means of the slit lamp if necessary with a contact glass with those made by means of ultrasound For a number of patients the optical examination of the vitreous body was not possible and in such cases the reason for this was noted In addition the ultrasound observations of the vitreous body in the affected eye were compared to observations of the other normal eye

The ultrasound apparatus used in the research consisted of an A scan instrument model 7100 A manufactured by Kretztechnik Austria and of a slightly focused transducer of 8 MHz/5 mm According to the author's own earlier observations (Oksala 1975) slight vitreous opacities and degenerations are more easily observable at a frequency of 6 MHz than at higher frequencies The power output control of the apparatus was equipped with a decibel scale from 0 to 80 and the examination always began with the maximum power output of the apparatus i e a dB reserve of 80

All the eyes suffering from acute anterior uveitis were examined in the initial stage of the disease when the patient entered the hospital For the examination the eye was anaesthetized by an eye drop after which the transducer was pressed against the sclera and the beam aimed at the vitreous

space from several different directions The results described here represent typical and easily repeated findings for each type of pathology

Results

Although the echoes reflected by *degeneration* of the vitreous body may sometimes resemble those from vitreous exudation the two are usually distinguishable Fig 1 A shows the echogram of the acoustically homogeneous vitreous body of a young subject in which the zero line indicates the vitreous space The echogram in Fig 1 B represents a case of degeneration + with a few separate low or high slowly moving echoes Fig 1 C shows the echogram resulting from a condition of degeneration ++ with numerous slowly moving low and/or hig echoes often forming echo clusters The echoes disappear from the screen when the power output is reduced by about 10–20 dB

The ultrasonic examinations of the vitreous body showed that echogram findings caused by *inflammatory exudation* could be divided into two categories according to their degree of severity (+ or ++) In the case of less severe acoustic modification of the vitreous body a few moving low echoes were observed separated from each other by shorter or longer zero lines Depending on the direction of the beam these echoes were observed either in the posterior part of the vitreous body or further to the front (Figs 2 A and B) These echoes usually disappeared from the screen when the power output was reduced by about 5 dB Inflammatory exudation could also cause more extensive acoustic changes in the vitreous space (Figs 2 C and D) in such a case moving echoes forming an almost continuous chain were reflected

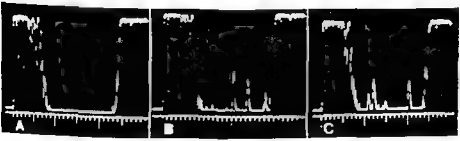

Fig 1 A B C

A Zero line indicates an acoustically homogeneous vitreous body
B Slight degeneration (+) appears in the vitreous body
C Severe degeneration (++) appears as numerous echoes and echocluster

As can be seen from Table I in 14 eyes the front of the vitreous body could not be examined by slit lamp the most usual reason for this was opacity of the anterior chamber (A C) and small pupil due to posterior synechias Exudation was revealed by slit lamp in the front part of the vitreous body in 11 eyes On the other hand an acoustic examination of the entire vitreous body was always possible In 4 cases the vitreous body was acoustically homogeneous but in these cases the examination by slit lamp was nevertheless impossible In 17 cases the vitreous body was acoustically highly opaque i e ++ and in seven of these it was impossible to compare optical and acoustic findings Of the other 10 six showed a good correlation between optical and acoustic findings In three eyes minor opacity of the vitreous body was indicated by ultrasound

In 19 patients the vitreous of the healthy eye was acoustically homogeneous six of the nine subjects who were over 50 years showed degeneration either + or ++ The ultrasound findings concerning the condition of the vitreous body in the affected and healthy eye were similar in subjects 4 / 10 15 and 25 i e in those cases in which both eyes showed either an acoustically homogeneous vitreous or a similar degree of degeneration

Discussion

On the basis of this and earlier studies (Oksala 1975) it is in most cases possible to distinguish the echograms of degeneration of the vitreous body on the one hand from inflammatory vitreous exudation on the other In degeneration the echoes are usually fewer their amplitudinal variations greater and their movement slower than in the case of exudation The differences are best visible on the screen of an oscilloscope This is of great clinical significance when vitreous changes are being observed in patients over 50 and in particular over 60 years of age

The acute iritis material presented here already shows that in this disease the optical examination of the vitreous body is often difficult or impossible In terms of the course and treatment of the disease however it is of great importance to know whether exudation is present in the vitreous and to what extent Furthermore even when optical examination is possible reliable observations are obtained only for the front of the vitreous body whereas the use of ultrasound provides equally good information for the whole of the vitreous body

In my experience acute allergic anterior uveitis with abundant exudation in the vitreous body can nowadays best be controlled in the initial stage of the disease by means of cortisone treatment both locally and systemically

As appears from the material presented here the ultrasound examination can allow us to determine whether there are also grounds for systemic cortisone treatment When the vitrous body shows acoustic changes due to exudation the use of ultrasound also permits us to follow quite reliable the effect of the treatment on the acoustic structure of the vitreous as well as on the disease itself

The extension of ultrasound applications from the diagnosis and localization of large scale and coarse acoustic changes such as intraocular tumours detachment of the retina and intraocular foreign bodies to the verification of vitreous degeneration and inflammatory changes will mean a remarkable broadening of clinical use This in turn will make its own demands in terms of apparatus Thus the ultrasound examination of tissues is significant not only in diagnostics but also in the treatment and follow up of diseases

References

Baum G & Greenwood I (1958) The application of ultrasonic locating techniques to ophthalmology II Ultrasonic slit lamp in the ultrasonic visualization of soft tissues *Arch Ophthal (Chicago) 60* 263–279

Baum et al (1975) *Fundamentals of Medical Ultrasonography* Putnam s Sons New York

Bellone E & Gallenga P E (1971) Ultrasonic features of changes in the vitreous body caused by degenerative inflammatory vascular and deforming diseases of the eye In Bock J and Ossoinig K Eds *Ultrasonographia medica* Vol 2 p 229–245 Wiener med Akademie Wien

Oksala A (1958) Ultraljudapparaten vid undersokning av ogat och dess sjukdomar *Nord Med 59* 731–733

Oksala A (1959) Ein Holzsplitter im Auge diagnostiziert durch Ultraschall *Klin Mbl Au enheilk 134* 88–93

Oksala A (1960) The echogram in vitreous opacities *Amer J Ophthal 49* 1301–1307

Oksala A (1969) A mode diagnosis of intraocular diseases In Wainstock M A Ed *Ultrasonography in Ophthalmology* p 543–572 Little Brown & Co Boston

Oksala A (1974) The influence of ultrasonic diagnosis on clinical ophthalmological examinations In deVlieger M et al Eds *Ultrasonics in Medicine* p 123–126 Excerpta Medica Amsterdam

Oksala A (1975) Ultraschalluntersuchung bei Synaresis des Glaskorpers Ultrasonography in Ophthal *Bibl ophthal 83* 78–85 Karger Basel

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ROD CONE INTERACTION SOME INDIRECT EVIDENCE

BY

P A ASPINALL

A group of diabetic patients were found to have losses in green blue colour discrimination and significantly early transition times in dark adaptation Analysis showed that the green blue losses were significantly related to early transition time Pre receptoral factors cannot account for these results but selective degeneration of the blue cone mechanism can The results are in agreement with a proposal of rod blue cone linkage after Trezona (1970)

Key words colour vision – dark adaptation – diabetes

In assessing the similarities and the differences between the rods and the blue receptors Trezona (1970) noted that the similarities (e g poor visual acuity similar spatial integration) were associated with the distribution and interconnection of the neural pathways whereas the differences (e g Stiles Crawford effect absorption curve) were associated with the receptor itself She proposed therefore that rods and blue cones existed as separate receptors but shared a neural pathway At intensities above the threshold of the blue cones the blue cones inhibited rod activity

Evidence for the inhibition of rods by cones is given by Clarke (1960) Aguilar & Stiles (1954) and Makous & Boothe (1974) in particular the inhibition of rods by blue cones is shown by Blackwell & Blackwell (1961) Hough (1968) Hough & Ruddock (1969)
Such a model was seen to be consistent with subjective effects such as the

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change in rod colour from neutral to blue with the scotopic to photopic transition and the Maxwell spot and was in keeping with modern opponent colours theory

It seemed plausible on the basis of this model that if an acquired dyschro matopsia selectively affected the blue mechanism then the inhibition of rod activity would be reduced In particular in an experimental procedure such as dark adaptation the reduced inhibition would enable rods to take over function at higher luminance levels so that the Purkinje shift would occur at an earlier stage into dark adaptation

One clinical entity well suited to test this hypothesis is diabetes Authors reporting yellow blue defects in diabetes include Zanen (1953) Dubois Poul sen & Cochet (1954 and Verriest (1964) More recently an extensive study of over 500 diabetics with age controls (Kinnear 1966 subsequently Lakowski Aspinall & Kinnear 1972) showed predominant losses in yellow blue and green blue discrimination In the following it is to be assumed that these yellow blue and green blue discrimination losses are an indication of selective damage to the blue mechanism in diabetes This is to be contrasted with the alternative assumption that the losses are due to selective pre receptoral absorption

Selective damage to the blue receptoral mechanism is inferred from three sources The first of these directly implicates receptor involvement while the remaining two provide suggestive evidence against the likelihood of pre receptoral absorption factors accounting for the colour discrimination losses

Firstly Lakowski et al (1972) showed that diabetics had losses in anomaloscope yellow blue and green blue matching ranges (MR) at all age groups but normal red green discrimination except in elderly diabetics The same pattern of results was present for diabetics with and without retinopathy although the former group had greater losses A Bayesian analysis of the follow up data on the state of the fundus five years after the colour vision testing showed that green blue matching ranges in diabetics without retinopathy could be used as a predictor of subsequent retinopathy (Aspinall 1973 Kinnear Aspinall & Lakowski 1972) If there is such a link between green blue losses and retinopathy it seems probable that the source of the green blue loss is in the retina itself

Secondly the same study showed that the anomaloscope mixture ratios (MMP) of diabetics under 35 years of age were the same as those of the age controls This *suggests that the receptor system* of most diabetics *is* genetically the same as the controls and that pre receptoral transmission is similar in the two groups (see Lakowski 1962)

Thirdly ophthalmoscopic examination of those diabetics under 40 years

who had good vision ($\leq$ 6/9) and no retinopathy did not reveal any sign of lens opacities or other changes in the occular media which could account for the yellow blue and green blue discrimination losses

Method

A group of 33 young diabetics (average age 27 years maximum 38 years) was selected by the Diabetic Out Patient department of the Royal Infirmary Edinburgh Only those patients with good visual acuity ($\leq$ 6/6 Snellen) and without retinopathy were included in the sample and a majority of patients (29) were on insulin therapy An ophthalmoscopic examination excluded from the sample any patient with pre receptoral abnormalities

The group was given a number of visual function tests including the F/M 100 Hue test the red green yellow blue and green blue equations of the Pickford Nicolson anomaloscope and a modified dark adaptation test (Aspinall 1974) This latter test produced two dark adaptation curves to two

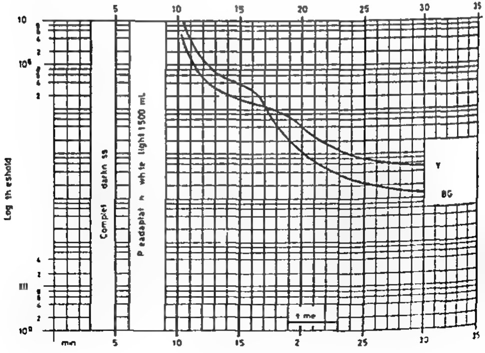

Fig 1
The dark adaptation procedure

filtered lights of 10° subtense centrally fixated (see Fig 1) Narrow band spectral filters from the Ilford range were used with peak transmissions at 560 and 505 nm Transmission values were adjusted with neutral density filters so that the dark adaptation curves to the two filters crossed over thus giving a clearly defined transition point between photopic and scotopic vision As only relative luminances were important no photometric calibration was necessary The luminance scale of the adaptometer (Goldmann Weekers) is calibrated as a varying source of white light and it was this luminance scale which was used in threshold measurements The preadaptation was white light at 1500 mL and 5 min duration

For the purpose of the analysis the absolute threshold for each curve at 2 min and at 20 min into adaptation was recorded together with the separation between the curves at these times and the cross over or α point It should be noted that the α point is arbitrarily defined i e by suitable choice of filters it is possible to arrange the point anywhere in the transitional phase (that phase where vision is neither purely photopic nor purely scotopic) However the emphasis rests upon a statistical comparison of the changes which occur between diabetic and normal vision The normal control group was a random sample of the general population Anomaloscope and FM 100 Hue norms were based on 89 normals and dark adaptation on 36 normals of equivalent age to the diabetic group

Results

The colour vision results (Table I) are comparable with those collected in the larger sample of Lakowski et al (1972) (discussed in the introduction) which may be considered as a more reliable index of diabetic performance on these tests In the present study the principal use of this data is for inter relations between tests

The dark adaptation results (Table II) show that the absolute threshold levels of the diabetics during the photopic and scotopic phases are not significantly different from normal In addition the cone separation between the curves at two min (0 23 log units) and the rod separation between the curves at 20 min (0 47 log units) are slightly smaller but not significantly different from those of the control group

A comparison of the cross over times shows that the diabetic group (mean = 4 84) does have a significantly earlier α point than the normals (mean = 5 70) on an uncorrelated t test ($t = 2\,24$ $P < 0\,05$) Thus although the absolute threshold levels are in the normal range the rods do take over function from

Table I
Colour vision in diabetics

		F/M 100 hue test	Colour vision: Anomaloscope equations: red green MR	red green MMP	yellow blue MR	yellow blue MMP	green blue MR	green blue MMP
Diabetic group								
N = 33	Mean	72 6	5 52	48 7	12 4	49 3	14 9	49 4
Mean age = 27 years	SD	38	2 9	3 2	6 3	2 9	9 0	[illegible]
Control group								
N = 89	Mean	56	4 8	49 3	3 9	49 ,	6 5	49 4
Mean age = 25 years	SD	54	2 0	2 8	3 0	2 5	3 5	[illegible]

Anomaloscope results are in j n d units

SD = Standard deviation MR = Matching range MMP = Mid matching point

the cones at an earlier stage into adaptation in the diabetic eye than in the normal eye

A comparison of the rates of rod adaptation was made to see if the early transition might be due to the faster dark adaptation of rods in diabetics. Because pupil diameter influences pre adaptation levels and subsequent dark adaptation rates measures of the pupil diameter were taken at a luminance of 100 cd/m in the diabetic and control groups but no significant differences found More importantly the rate of rod adaptation in the two groups was compared by noting the time taken to reach a fixed threshold level (4 0 log units) This was 10 9 min for the green blue diabetic curve and 10 5 min for the green blue control curve a difference which was not significant

The cone adaptation rates of the two groups were compared by noting the time to reach a fixed threshold level of 6 0 log units The times were 2 min for the control group and 1 8 min for the diabetic group Because of a significant F ratio of the variances in the two groups a median test was used but no significant differences between the times in the two groups was found

Correlations within the colour vision tests showed that the yellow blue and green blue matching ranges were significantly related (r = 0 81 $P < 0 01$) as were their corresponding mid matching points (r = 0 63 $P < 0 01$) The red green matching range was not related to either the yellow blue or the green blue matching ranges In dark adaptation significant correlations were found between the cone thresholds (Y2 and BG2 r = 0 75 $P < 0 01$) and between the rod thresholds (Y20 and BG20 r = 0 84 $P < 0 01$)

Correlations between the matching ranges of the three anomaloscope equations and dark adaptation threshold (Y2 BG2 Y20 BG20) were not significant Correlations between the cross over time and the matching ranges were also not significant although there was some indication that the larger yellow blue and green blue matching ranges were associated with earlier cross over times A further analysis was carried out by comparing the matching ranges corresponding to the extreme values of the cross over time (i e the earliest and the latest ten cross overs) using the Mann Whitney U test A significant difference was found between the two sets of green

Table II
Dark adaptation in diabetics

		Dark adaptation						
		Absolute thresholds				Cone separation	Rod separation	Cross over α point
		(log units)				(log units) (BG2–Y2)	(log units) (Y20–BG20)	(min)
		Y2	BG2	Y20	BG20			
Diabetic group								
N = 33	Mean	5 71	5 94	3 /8	3 31	0 23	0 47	4 84
Mean age = 27 years	SD	0 19	0 29	0 22	0 23	0 09	0 12	1 /
Control group								
N = 89	Mean	5 /5	6 00	3 58	3 10	0 25	0 48	5 0
Mean age = 25 years	SD	0 15	0 17	0 10	0 16	0 03	0 02	0 90

Y2 Threshold to yellow filter at 2 min into adaptation
Y20 Threshold to yellow filter at 20 min into adaptation
BG2 Threshold to green blue filter at 2 min into adaptation
BG20 Threshold to green blue filter at 20 min into adaptation

blue matching ranges ($P < 0.05$) The equivalent comparison for the yellow blue equation just failed to reach significance while that for the red green equation showed no significant difference

Finally the ratios of the discrimination ranges on the three anomaloscope equations were calculated for each patient and correlated (Spearman rank) with the cross over times over the whole group The correlation between the ratio of green blue to red green discrimination and the cross over point was equal to -0.40 ($P < 0.02$) that between the ratio of yellow blue to red green discrimination and the cross over point was equal to -0.29 ($P < 0.05$) and that between the ratio of green blue to yellow blue discrimination and the cross over point was equal to -0.02 ($P > 0.05$) Therefore a relative green blue or yellow blue to red green discrimination loss was significantly related to early cross over times in dark adaptation (To enable a comparison across the three anomaloscope equations a common measuring scale was calculated by transforming the arbitrary anomaloscope data into the C I F UCS (1960) - Lakowski & Aspinall (1972))

Discussion

A group of young diabetics with good visual acuity and without retinopathy were found to have losses in yellow blue and green blue colour discrimination without concomitant losses in red green discrimination The group also had a significantly early cross over time in dark adaptation without significant differences in the absolute threshold levels during the photopic and scotopic phases The early cross overs were associated with extended matching ranges in green blue discrimination Evidence that it was specifically green blue discrimination which was related to cross over time was found by correlating the ratio of green blue to red green matching ranges with the a point Significant correlations showed that the greater the relative green blue or yellow blue to red green loss the earlier the transition from photopic to scotopic vision If it can be assumed that the anomaloscope green blue and yellow blue losses are a measure of selective blue cone degeneration (see introduction) the results are in agreement with a proposal of rod blue cone linkage (Trezona 19 0)

It will be recalled that the anomaloscope field subtends 2 whereas the dark adaptation test patch subtends 10° both fields being centrally fixated Consequently the transition point in dark adaptation must occur when rods in a 10 central retinal area become more sensitive than either foveal or parafoveal cones The relative sensitivities of dark adapted cones within

± 5° of the fovea appear to be similar providing test patch wavelengths longer than 500 nm are used which avoid absorption by the macular pigment (Wald 1960) Furthermore as the evidence of blue cone damage is based upon a central 2° field it would appear necessary for the inhibitory hypothesis to assume that blue cones are selectively damaged throughout the central 10 field or throughout the whole retina Such a view is not unlikely if the retina is uniformly exposed to the basic underlying metabolic defect of diabetes

The possibility that the colour discrimination losses (and early cross over times) are due to pre receptoral transmission factors has been discounted in the introductory section There is an additional reason for doing so from the evidence of the dark adaptation thresholds If a selective yellow filtering is proposed to account for the colour discrimination losses such a filter should have a greater relative effect on the green blue than on the yellow adaptation curve The thresholds to green blue in both cone and rod sections of the dark adaptation curve should be raised by a fixed amount corresponding to the increased optical density to the green blue light The result would be later not earlier transition times an increase in cone separation and a decrease in rod separation between the curves Indeed normal age changes in dark adaptation to the two lights used in this study have precisely this effect (see Aspinall 1974) However in the diabetic case neither the transition times nor the cone and rod separations differ from normal in this way

As a supplementary note on the rod cone relationship proposed in this paper the author found in a general study of acquired dyschromatopsias over a variety of clinical conditions that the early cross over time only occurred in cases where scotopic function was normal and where green blue losses were present On the other hand patients with late cross over times tended to have scotopic losses and more generalised deterioration in colour vision It may be the case therefore that early transition times result from a degeneration of the cones while rod function remains normal The photophobia experienced by several patients with abnormally early cross over times may be related to the rods firing at abnormally high luminance levels so producing a type of discomfort glare

Acknowledgment

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References

Aguilar M & Stiles W S (1954) Saturation of the rod mechanism of the retina at high levels of stimulation *Optica Acta 1* 59–65

Aspinall P A (1973) *Bayes Theorem The Logic of Diagnosis?* Visual Lab Report Edinburgh University

Aspinall P A (1974) A two filter method for dark adaption study *Ophthalmologica 169* p 299

Blackwell H R & Blackwell O M (1961) Rod and cone receptor mechanisms in typical and atypical congenital achromatopsia *Vision Res Vol 1* p 62

Clarke F J J (1960) Extrafoveal colour metrics *Optica Acta 7* 355–384

Dubois Poulsen A & Cochet P (1954) Un cas de dyschromatopsie diabetique *Bull Soc Ophthal France 4* 323–330

Hough E A (1968) The spectral sensitivity functions for parafoveal vision *Vision Res 8* 1423–1430

Hough E A & Ruddock K (1969) The Purkinje shift *Vision Res 9* 313–316

Kinnear P R (1966) *The colour discrimination of diabetes* M Sc Thesis Edinburgh University

Kinear P R Aspinall P A & Lakowski R (1972) The diabetic eye and colour vision. *Trans ophthal Soc U K 92* 69–78

Lakowski R (1962) Is the deterioration of colour discrimination with age due to lens or retinal changes? *Farbe 2* 69–86

Lakowski R & Aspinall P A (1972) Transformation of arbitrary anomaloscope data to the C I E system of specification *Optica Acta 19* 5 399–402

Lakowski [redacted] Aspinall P A & Kinnear P R (1972) Association between colour vision losses and diabetes mellitus *Ophthal Res 4* 145–159

Makous W & Boothe R (1974) Cones block signals from rods *Vision Res 14* p 285

Trezona P W (1970) Rod participation in the blue mechanism and its effect on colour matching *Vision Res 10* 317–332

Verriest G (1964) Les deficiencies acquises de la discrimination chromatique *Mem Acad roy Med Belg 2/3* 5 35–327

Wald G (1960) Analysis of Retinal Function by a Two Filter Method *J opt Soc Amer 50* p 633

Zanen J (1953) Introduction a l etude des dyschromatopsias retiniennes contrales acquises *Bull Soc Ophtal Belg 103* 3–145

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IMMOBILIZATION OF THE EYE

Evaluation of a New Method in Retinal Detachment Surgery

BY

PEEP ALGVERE and BENGT ROSENGREN

Experiments on eye phantoms (closed chambers filled with suspensions of lipoid particles in water) have shown that saccadic rotational movements induce liquid currents flowing back and forth through a hole in a latex membrane mounted inside the chamber It is postulated that rapid (saccadic) eye movements generate similar motions in the liquid vitreous capable of moving a detached retina

Sixty five non selected eyes with primary rhegmatogenous retinal detachment were immobilized by traction sutures usually for 2–3 days (range 1–5 days) prior to surgery An almost complete spontaneous reattachment occurred in 45 % of the cases a partial reattachment (i e more than half of the detached area) was seen in 37 % but no reattachment took place in 18 % This rate of reattachment is higher than that obtained by bilateral eye patching and complete bed rest

Rapid (saccadic) eye movements are considered to be one crucial factor counteracting retinal reattachment Eyes in which preoperative reattachment is achieved can be cured by simple surgical procedures and have a favourable progno is

Key words retinal detachment – human eye – ocular immobilization – traction sutures – spontaneous reattachment – prognosis

The sealing of the retinal break – the thesis of Jules Gonin – remains the foundation of the surgical treatment of rhegmatogenous retinal detachment (Gonin 1934) A prerequisite for healing is that a firm adhesion is established

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between the neuro retina and the pigment epithelium or choroid around the break Such adhesion is achieved only if the subretinal fluid is eliminated

Reattachment of the retina can be attained in several ways In some cases bed rest and bilateral eye patching enable the retina to reattach spontaneously whereupon chorioretinal adhesions or scarring can easily be produced by photo coagulation or by cryo applications Reattachment however is regularly achieved if the retinal break is sealed by a local scleral buckling procedure as first described by Custodis (1951) or by an encircling technique as introduced by Schepens et al (1957)

The closing of the retinal break generally results in a rapid elimination of the subretinal fluid This implies that the absorption capacity normally present is sufficient to drain the subretinal fluid when the liquid flow (from the vitreous) through the retinal break is blocked (Rosengren 1971 1972) The question arises whether this flow can be wholly or partially prevented by other means This thought led to the development of a procedure *inhibiting* the liquid currents in the vitreous space by the immobilization of the eye

In experiments designed to illustrate hydrodynamic effects in the vitreous space Lindner (1933) noted that *rotational* movements of a spheric glass flask filled with water induced distinct wavy motions of the free flags of a perforated membrane mounted inside the container *Translational* movements on the other hand did not produce such an effect These observations were confirmed in experiments performed

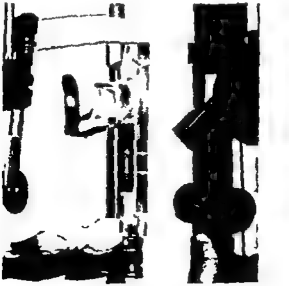

Fig 1
The cylindrical glass container attached to the slit lamp

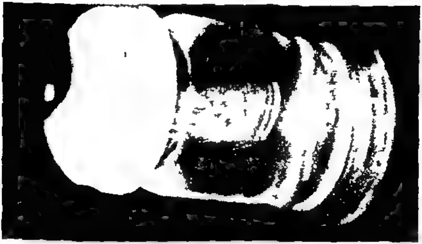

Fig 2

Movements of the lipoid particles suspended in water as seen in the optical section

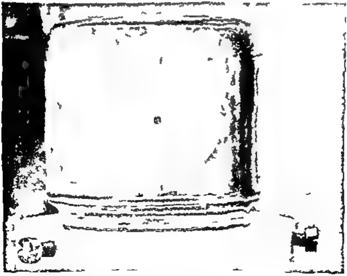

Fig 3

The container equipped with a latex membrane showing the central hole

with a closed chamber about the size of the eye filled with water and suspended cotton fibers (Rosengren 1974) The liquid currents were further analyzed by observing suspended particles in the fluid with a slit lamp (Rosengren & Osterlin 19 6) On rapid saccadic rotational movements a liquid flow is induced most conspicuously visible in the circular periphery of the container (Figs 1 2)

In order to study the effects of such a liquid flow a latex membrane (0 1 mm thick and 45 mm in diameter) with a central hole (2 mm in diameter) was mounted inside a cylindrical container and its edges glued to the circular wall (Fig 3) The container (volume 175 ml) was filled with a suspension of lipoid particles in water On saccadic rotational movements of the container wavy motions of the latex membrane were observed with the slit lamp There was also a liquid flow back and forth through the central hole in the membrane (Fig 4) Following translational movements of the container there was no liquid flow through the hole nor were there any wavy motions of the membrane itself

These observations raise the question as to whether rotational liquid motion causing flow through a retinal break may prevent reattachment of a detached retina We have therefore conducted a clinical study to determine whether a detached retina will reattach following immobilization of the eye

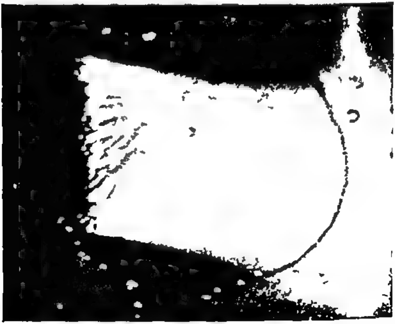

Fig 4
Liquid flow as revealed by the motion of lipoid particles through the hole in the latex membrane

Case Material

Immobilization of the eye by means of traction sutures was carried out in 67 patients consecutively admitted to the Retina Service for primary rhegmatogenous detachment. Satisfactory notes on the preoperative reattachment are lacking for 2 patients (one surgical success, one failure), and these eyes are excluded from the study.

The remaining material consisted of 23 males and 42 females. The patients' ages ranged from 8 to 80 years, the mean being 56 years. Thirteen eyes were aphakic. In the phakic eyes the refraction ranged from +5 D to –30 D.

The duration of the detachments varied from one day to about one year (median 11 days). Seven eyes had been operated on before, the rest underwent retinal surgery for the first time.

The detachment covered less than 90° of the fundus in 13 eyes, 90–180° in 37 eyes and extended to more than 180° in 15 eyes. In 50 eyes there were retinal tears in the upper quadrants of the fundus, and 10 eyes had retinal breaks only in the lower quadrants. In 5 eyes no retinal breaks were found; 4 of these were aphakic eyes and the 5th one had been operated on four times before.

Each patient appears in this case material only once, i.e. the first time the patient was admitted to the hospital for retinal detachment during the one year period of study. During this same period 2 additional patients with retinal detachment were admitted to the Retina Service but not treated with immobilization by traction sutures (and not included in this study). One eye had previously been operated on for strabismus and the other patient had a purulent conjunctivitis.

Methods

In the first 15 patients treated, the eyes were immobilized by one traction suture placed under the inferior rectus muscle and the eye was rotated upwards. It was soon realized, however, that this measure usually inhibited most of the vertical movements of the eye but not the horizontal ones. Therefore, in the following cases, an additional suture was placed under the medial rectus muscle and the eye was rotated upwards and laterally and fixed in maximal elevation, as previously described (Algvere & Rosengren 1976).

The standard procedure is as follows. The conjunctiva is incised near the insertions of the inferior and medial rectus muscles respectively. A muscle hook is inserted under the whole muscle belly and a Ticron (3–0) suture is placed under the muscle

Fig 5

A The eye is immobilized by traction sutures placed under the inferior and medial rectus muscle respectively The suture from the medial rectus is pulled laterally and affixed to the skin of the temporal region The suture from the inferior rectus is pulled upwards and affixed to the skin of the forehead The eye is thus rotated laterally and immobilized in maximal elevation B Patient using her fellow eye without difficulty

Each of the two traction sutures is then tied around a small wooden stick which is affixed to the skin of the forehead by tape (Fig 5) It is essential that the eye is rotated maximally and the sutures pulled and affixed firmly If the traction is in sufficient the jerky ocular movements continue and the procedure is useless To prevent infection the skin of the forehead and the eye brow should be cleaned as for surgery Atropine (1 %) eye drops and Chloromycetine ointment are given daily

The sutures were usually left in place for 2–3 days (range 1–5 days) The fellow eye was not covered and the patient was not restricted to bed rest In cases of very high bullous detachments particularly in the upper quadrants of the fundus the patient was instructed to remain in bed most of the day with the head in a flat position A stenopaeic disc (aperture 1 mm) in front of the fellow eye was used in some of these cases (this was done to reduce the tendency towards rapid saccadic movements) It must be pointed out however that all patients were allowed to walk to the bathroom and to the table for meals

Postoperatively one traction suture was replaced under the inferior rectus muscle and usually kept for 3–5 days (range 3–7 days) Even during the post operative period patients were not confined to bed

Procedures in retinal detachment surgery

The standard procedure comprised cryo application and an episcleral buckle made of a silicone rubber rod cut to a half cylinder In giant retinal tears particularly in large dialyses and in aphakia and high myopia encircling procedures were often used (a silicone rubber rod 2 mm teflon band or Arruga suture combined with silicone rods)

In cases where the retinal break was not blocked by the buckle the sub retinal fluid was drained through a 2–3 mm sclerotomy in a procedure similar to that described by Freeman & Schepens (1974)

Results

The rate of reattachment is based on 65 non selected cases of primary rheg matogenous detachment of the retina that were consecutively admitted to the hospital In 27 of the 52 phakic eyes there was a complete or almost complete preoperative reattachment of the retina (Table I) By almost complete re attachment we mean that a bullous detachment had disappeared but a flat elevation remained around the retinal break The course of the reattachment was rapid in many eyes Several high bullous detachments reattached almost completely within 2–3 days (Fig 6) There was no subretinal fluid to drain at surgery in these 27 cases

In 20 phakic eyes there was a partial reattachment i e at least half of the detached area reattached and only a very flat detachment persisted (Table I) For example a high bullous detachment in the upper quadrants of the fundus flattened leaving only a circumscribed low detachment (Fig 7) There is obviously a gradual transition from the partial reattachment to the complete one (Fig 8) If the immobilization by traction sutures had been

Table I

Spontaneous reattachment after fixation of the eye with traction sutures

	Almost complete reattachment	Partial reattachment	Little or no reattachment
Aphakia	2	4	7
Phakic eyes	[illegible]	20	5
	[illegible] (45 %)	24 (3[illegible] %)	12 (18 %)

Fig 6

A Fundus photograph (45° view) of a bullous retinal detachment due to an equatorial tear at the 10 o clock meridian. B The detachment disappeared 2 days after ocular immobilization with traction sutures when the patient was in a supine position m st time of the day Male aged 55 years

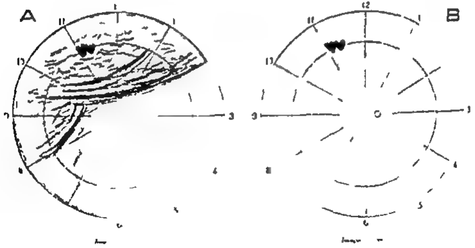

Fig 7

Fundus drawings illustrating a partial reattachment of the retina i e more than half of the detached area The initial detachment (A) flattened after 3 days of ocular immobilization leaving a low detachment around the equatorial breaks at the 11 o clock meridian (B) Female aged 0 years

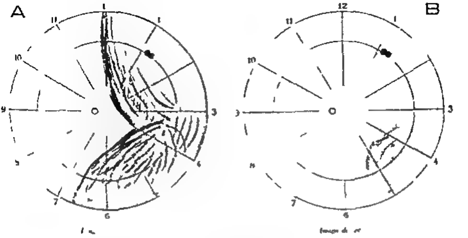

Fig 8
The detached retina (A) reattached around the retinal break 5 days after ocular immobilization leaving some residual subretinal fluid in the lower temporal quadrant (B) Fundus drawings of a 75 year old female

continued for a few more days some partial reattachments would probably have reattached completely However it was not necessary to prolong the immobilization because at this stage despite only partial reattachment the eyes responded favourably to surgery In order to close the retinal breaks and to achieve complete reattachment at the end of the operation the subretinal fluid had to be drained in 11 cases

In aphakia the frequency of reattachment appears to be considerably lower In 7 of 13 aphakic eyes there was no tendency towards reattachment (Table I) Detachments with heavy vitreous retraction belong to this group Our study includes 3 such eyes in which a vitreous hemorrhage and retraction with retinal detachment were seen about one week after intracapsular cataract extraction Those cases in which little or no reattachment occurred are listed in Table II

It was also observed that in phakic eyes a delayed absorption of subretinal fluid was associated with fixed retinal folds which kept the retinal break open The size of the horse shoe tear has no decisive effect on reattachment and large tears may well reattach although this will take a few days longer (Fig 9) In giant dialyses of the ora serrata (3 cases) little tendency towards reattachment was observed even though the eyes were immobilized for 5 days

Table II

Little or no tendency toward reattachment following fixation of the eye (12 patients)

	No of eyes
Aphakia	
Vitreous hemorrhage and retinal detachment seen 1 week after intracapsular cataract extraction	5
Ora dialysis (90°) in upper medial quadrant with dislocated lens (Marfan's syndrome)	1
Ora dialysis in the 5–7 o'clock meridians	1
Bullous detachment with 4 equatorial breaks in upper quadrants	1
Peripheral horse shoe tear (about 2 mm) at the 1 o'clock meridian with vitreous adhesion	1

Phakic eyes	
Progressive myopia (–30 D) with 270° ora dialysis	1
Ora dialysis (60°) in upper lateral quadrant of 80 years old man	1
Massive vitreous retraction 8 months after photocoagulation of retinal tear without detachment	1
Two retinal tears with traction in inferior quadrants	1
Horse shoe tear at the 1 o'clock meridian (insufficient immobilization?)	1
	5

The *postoperative* ocular fixation seems to secure the retina in the favourable position obtained by surgery (i e in contact with the pigment epithelium) during the initial period of healing of cryo or photo effects In a routine case the patient was discharged about one week after surgery

The preoperative reattachment of the retina can be related to prognosis In eyes where the retina reattached prior to surgery the rate of primary healing (i e the results obtained to date) was high (Table III) The marked difference in surgical success between phakic and aphakic eyes was clearly demonstrated However the follow up period was short ranging from 2 to 14 months from the last operation (where more than one was performed) and further recurrences may occur

Fig 9

Fundus photograph (45° view) of large retinal tear (A) and bullous detachment in upper quadrants (B) in myopic eye (-10 D) of a 4? year old woman There was a partial reattachment after 5 days of ocular immobilization Then the traction sutures were removed (for photography) and the retina redetached within minutes

Complications

Following the use of traction sutures certain complications were observed During the first postoperative weeks some patients had vertical diplopia and many had a hyperphoria both of which gradually subsided No patient has

Table III
Primary healing following surgery of retinal detachment
(65 patients follow up time 2-14 months)

	Almost complete reattachment	Partial reattachment	Little or no reattachment	Total
Phakic eyes	2/2	3/4	3/7	8/13 (61 %)
Aphakia	7/27	18/20	3/5	48/52 (92 %)
	29/29	21/24	6/12	56/65 (86 %)

yet required a surgical correction of these symptoms Traction sutures may make the eye more susceptible to infections In a eyes a purulent conjunctivitis developed

Discussion

As has been demonstrated in hydrodynamic experiments using eye phantoms (closed chambers filled with water) rapid rotational movements resembling the ocular saccades induce considerable liquid currents capable of movin or even detaching a perforated latex membrane from inside the chamber Although basic differences exist between experimental chambers and the living eye it seems reasonable to assume that on rapid eye movements rotational liquid currents are similarly generated in the fluid vitreous These currents can move the formed vitreous and a detached retina When the saccadic eye movements are inhibited by ocular immobilization such liquid currents may cease as does the wavy motion in the detached retina

The present work shows that following immobilization of the eye the retina reattached spontaneously (completely or partially) in about 82 % of the cases although the patients were not confined to bed It is assumed that the never ceasing rotational liquid flow moving back and forth in the periphery of the vitreous space is one crucial factor counteracting retinal reattachment This factor was probably eliminated by immobilization of the eye

This rate of preoperative reattachment is higher and achieved in a shorter time than that obtained without active immobilization of the eye Hofmann & Hanselmayer (1973) reported on 312 cases treated with bilateral eye patching and complete bed rest for 1–12 days (i e 70 7 % of their case material of 441 retinal detachments) There was a practically complete reattachment in 28 1 % a significant flattening of the retina in 24 4 % a slight flattening in 27 9 % and no effect in 19 6 % However eyes are generally not immobile under patches and considerable eye movements do occur as shown by electronystagmography (Ericson & Fluur 1961)

The ocular immobilization is most valuable in cases with high bullous detachments where the retinal break cannot easily be sealed with a buckle since the neuro retina remains too far from the pigment epithelium A complete or partial reattachment prior to surgery is advantageous in several ways and makes for a favourable prognosis Localization of the retinal break by ophthalmoscopy and indentation with the cryo probe are facilitated during the operation the break being close to the pigment epithelium (and to the sclera) As a result it is easy to place the scleral buckle exactly over the break Consequently the buckles can be made small and tailored to the size of the retinal

break A small buckle can more readily produce a deep indentation and is likely to remain in the desired position The amount of subretinal fluid if present at all is minimal and there is little if any need for drainage Even light cryo applications will reach the neuro retina and their effect will not be limited to the pigment epithelium and choroid as in high retinal detachments

Recent studies on monkeys have shown that when only the pigment epithelium was treated by cryo the neuro retina being detached the resulting adhesion when reattachment was accomplished lacked the microvillous interdigitations normally present between pigment epithelial and other retinal cells (Laqua & Machemer 1976) Such an incomplete adhesion is probably not very strong On the other hand when treatment was also applied to the neuro retina true cell junctions developed between retinal cells and the pigment epithelium producing a stronger adhesion

A reattachment prior to surgery indicated that the vitreous strands or membranes were apparently not sufficiently strong to prevent reattachment The surgical need for reinforcement of retinal adhesion and counteraction of vitreous traction is no major problem in such cases On the other hand in eyes where preoperative reattachment was not achieved vitreous traction with fixed retinal folds may have been present In these cases vitreous traction must be treated properly with a permanently high buckle preferably secured with an encircling element

References

Algvere P & Rosengren B (1976) Active immobilization of the eye in the treatment of retinal detachment *Mod Probl Ophthal 18* Karger Basel (in press)

Custodis E (1951) Beobachtungen bei der diathermischen Behandlung der Netzhaut ablosung und ein Hinweis zur Therapie der Amotio retinae *Ber dtsch ophthal Ges* 57 222–230

Ericson L A & Fluur E (1961) Electro oculographic studies during treatment for retinal detachment *Acta ophthal (Kbh) 39* 222–250

Freeman H M & Schepens C L (1974) Innovations in the technique for drainage of subretinal fluid Transillumination and choroidal diathermy *Trans amer Acad Ophthal Otolaryng 78* OP 829–836

Gonin J (1934) *Le decollement de la retine pathogenie – traitement* Payot Lausanne

Hofmann H & Hanselmayer H (1973) Ablatio retinae Ausmass und Haufigkeit der Wiederanlegung durch praoperative Ruhigstellung *Klin Mbl Augenheilk 169* 178–185

Laqua H & Machemer R (1976) Repair and adhesion mechanisms of the cryotherapy lesion in experimental retinal detachment *Amer J Ophthal 81* 833–846

Lindner K (1933) Über die Herstellung von Modellen zu Modellversuchen der Netz hautablosung *Klin Mbl Augenheilk 90* 259–300

Rosengren B (1971) Significance of subretinal absorption for effectiveness of buckling operation *Acta ophthal (Kbh)* 49 866–872

Rosengren B (1972) Role of absorption in the subretinal space for the symptoms and surgery of retinal detachment *Mod Probl Ophthal* 10 60–65 Karger Basel

Rosengren B (1974) *Modellforsok for belysande av stromningar i glaskroppen vid ogats rorelser* Svenska Ogonlakareforeningens forhandlingar p 4–5 Stockholm

Rosengren B & Osterlin S (1976) Modellversuche zur Beleuchtung der Entstehung der Elevation bei Netzhautablosung *Ber dtsch ophthal Ges* (in press)

Rosengren B & Osterlin S (1976) Hydrodynamic events in the vitreous space accompanying eye movements Significance for the pathogenesis of retinal detachment *Ophthalmologica 173* 513–524

Schepens C L Okamura R J & Brockhurst R J (1957) The scleral buckling procedures I Surgical technique and management *A M A Arch Ophthal 58* (9) 311

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THE OPTICAL FUNCTION OF KERATOPROSTHESES

BY

A SOKOL T I BERTELSEN and N TEIGLAND

The optical function of acrylic cylinders used in keratoprostheses is demonstrated by using a water filled minicamera as a model of the aphakic human eye Lengths and diameters of the optical cylinders are important factors influencing the visual fields The dimensions to be chosen depends on the thickness of the cornea and the supporting tissues The most suitable combination of visual field magnification and diameter of the retinal image field is obtained with optical cylinders with a concave posterior surface Using a fixed radius of curvature of the posterior surface the radius of the anterior surfaces are calculated to make the eye emmetropic With such a cylinder of length 4 5 mm and diameter 2 1 mm a circular visual field of 48 is obtained With cylinder length 6 0 mm the visual field is at least 55 The retinal image is about 19 % larger than that of the normal phakic eye Cylinder length exceeding 6 0 mm require a greater diameter to provide an adequate visual field With cylinder lengths up to 6 0 mm and diameters not less than 2 1 mm the diameter of the retinal image field is at least 1? 0 mm Accidental obliquity of the optical cylinder or off center implantation give the possibility of undesired projection of the image field outside the macula The obliquity or degree of off center implantation tolerance is calculated The retinal image may be improved by darkening the side of the cylinder

Key words Keratoprostheses optical function

The problems concerned with the insertion of an optical prosthesis in the cornea in patients who have had no benefit from conventional surgery are due first of all to the difficulties of obtaining permanent retention of the pros

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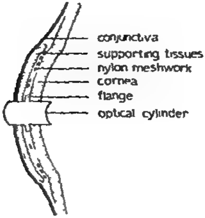

Fig 1
Sagittal section of the anterior part of an eye with a keratoprosthesis *in sit*

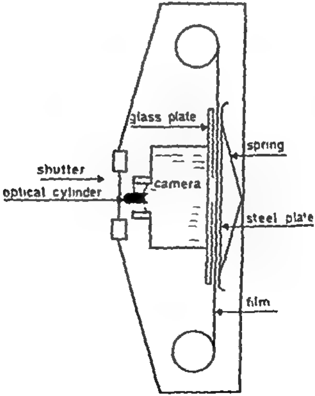

Fig 2
Schematic presentation of the water filled minicamera

thesis Another problem if the prosthesis is not extruded is that the tissues of the eye have a tendency to encapsulate it so that its front and back surfaces become covered To try and overcome these difficulties keratoprostheses with different modes of fixation have been designed (Cardona 1962 1969 Strampelli 1963 Choyce 1970 Bertelsen & Syversen 1973) Common to most of the pros theses however is an optical system which consists of a through and through optical cylinder made of methylmethacrylate in which the ends of the cylinder are the refracting surfaces replacing the refraction of the cornea and the lens (Fig 1) Insertion of such an optical cylinder in the cornea will for several reasons give different optical conditions from those resulting from a successful corneal graft

The refractive index of methylmethacrylate which the optical part of the prostheses usually are made of is considerably higher (1 49) than that of the normal cornea (1 376)

The distance between the refracting surfaces of an optical cylinder is much greater than in the cornea The cylinder has to be made long enough to project beyond the surfaces of the cornea to prevent overgrowth of the sur rounding tissues Optical cylinders with a length of 4–6 mm have been used

In order to minimize the contact between the optical cylinder and the surrounding tissues thereby reducing the extrusion rate the cylinder usually has a small diameter If the thickness of the cornea and supporting tissues totals 2 mm (Fig 1) a reduction in diameter of the cylinder from 3 mm to 2 mm will cause a reduction of the contact surface from 18 84 mm to 12 56 mm *i e* 33 % Cardona (1962 1969) has used cylinders with diameters 1 5 mm to 2 5 mm Strampelli (1963) 2 25 to 2 75 mm Choyce (1970) 3 5 to 4 5 mm Girard et al (1969) 3 17 mm Lund (1972) 2 0 mm and Bertelsen & Syversen (1973) 2 1 mm

Light coming in through the side of the anterior prominence of the cylinder and reflections of light from the side of the cylinder may disturb the image formation

Previous literature on keratoprostheses has not dealt in much detail with the optical function Hruby (1970) has suggested that the usual types of pros theses give such a small image on the retina that the poor visual results in some of these patients may possibly be due to improper positioning of the optical cylinder causing image projection outside the macula

There are no agreement on the optimal refractive power of the optical cylinders Girard et al (1969) used cylinders with refractive power of 26 D and Cardona (1969) 56 D Lund (1972) has used cylinders of 42 to 65 D in aqueous humour Bertelsen & Syversen (1973) have used cylinders which were made individually after ultrasonographic measurements of the axial lengths

Table I

Properties of the optical cylinders used in the *experiments* and the resulting visual fields and retinal image fields

Cylinder No	Length mm	r_1 mm	r_2 mm	Refractive power in diopters		Magnific per cent in exper	Visual field in degrees			Diameter of retinal image field in mm		
				in air	in exper		Φ1.5 mm	Φ2.1 mm	Φ3.1 mm	Φ1.5 mm	Φ2.1 mm	Φ3.1 mm
1–3	4.5	7.24	6.80	10.4	49.3	18.5	34	48	70	13	19	32
4–6	6.0	7.43	6.80	13.0	49.0	19.6	21	35	58	8	14	24
7–9	10.0	7.89	6.80	20.1	48.6	20.5	10	19	35	4	7	14
10	6.0	11.9	−10.00	32.9	53.3	6.0		37			12	
11	6.0	9.33	~	39.6	52.6	11.4		37			13	
12	4.5	~	~									

of the eyes and with a refractive power calculated to make the eyes emmetropic

The purpose of this work has been to study the influence the length diameter shape of the refracting surfaces and the transparency of the side of the optical cylinder may have upon the size and the quality of the retinal image and on the extent of the visual field The eligibility of individual designed optical cylinders and the importance of a proper alignment of the cylinder in relation to the optical axis of the eye has also been investigated

Material and Methods

A fluid filled micro camera with an optical system consisting of interchange able cylinders of the type used in prosthokeratoplasty has been constructed (Fig 2) In all the optical cylinders examined the distance from the anterior surface to the point which was designed to be on a level with the anterior surface of the cornea was 2 mm The length of the camera from this point to the film was 24 mm The fluid in the camera during these trials has been distilled water which has a refractive index of 1 333 (The refractive index of aqueous humour and vitreous humour is 1 336) As keratoprosthesis operations are as a rule carried out on aphakic eyes we have only examined optical cylinders designed for such eyes We have used 12 different optical cylinders in our trials (Table I) The diameters of the cylinders were 1 5 2 1 and 3 1 mm and the lengths 4 5 6 0 and 10 0 mm Most of the cylinders (Nos 1–9) were provided with a concave posterior surface with the same radius of curvature as the posterior surface of the average normal cornea 6 8 mm In addition one biconvex (No 10) one planoconvex (No 11) and one cylinder with flat end surfaces (No 12) were tried

With a fixed radius of curvature of the posterior surfaces (r) of the cylinders the curvatures of the anterior surfaces needed to make this model of an aphakic eye emmetropic have been calculated according to the following formula

$$r_1 = \frac{n_k - n}{n_k} \quad \frac{(L + n_L a^1 \qquad)}{n \; - D_{wk} \quad a^1}$$

r_1	=	radius of curvature of the anterior surface of the cylinder
$n_k = 1\ 49$		refractive index of methylm thacrylate (optical cylinder)
$n = 1\ 0$	–	refractive index of air
$n = 1\ 333$	=	refractive index of water
a^1	=	distance between the posterior surface of the optical cylinder and the image

D_{wk} = dioptric power of the posterior surface of the optical cylinder in water $= \frac{n_w - n_k}{r}$

L = length of the optical cylinder

r = radius of curvature of the posterior surface of the optical cylinder

The dioptric power of each cylinder in situ can then be calculated according to the following formula

$$D = \frac{n_k - n_a}{r_1} + \frac{n - n_k}{r} - \frac{L}{n_t} \quad \frac{n_a - n}{r_1} \quad \frac{n_w - n_k}{r}$$

A black and white film (Kodak Verichrome PAN) with a light sensitivity of 22 DIN was used for the experiments Using this model of the aphakic eye we have photographed a white screen with a black cross surrounded by concentric circles and also a chart of Snellens test types at a distance of 1 m The circles represented angles of 7 5° 15° and 30° as measured from the centre similar to an ordinary visual field screen As the visual fields in these patients are circular the angular value of the total visual field has the double magnitude

The screen was illuminated by two 500 W photo lamps placed at a distance of 2 m The exposure time was 1 25 seconds Pilot trials not described here have shown no difference in detail resolutions of films taken at 6 m and 1 m distance when the camera was adjusted for infinity We have therefore used this camerasetting in all our trials

To judge the relative aperture of the optical cylinders a scale of grey shades has also been photographed By comparing the pictures taken by conventional photography with known aperture ratio with the pictures taken in this way one has got an indication of the relative apertures of the cylinders

The focal depth was examined by photographing the same object at a distance of 1 m and a distance of 0 33 m without altering the camera setting *All the measurements and conclusions refers to the original films* Copying and re photographing have however reduced the quality of the illustrations somewhat

Results

The combinations of radii of curvatures of the surfaces needed to make this model of an aphakic eye emmetropic and the resulting dioptric powers of the optical cylinders used in these experiments are summarized in Table I

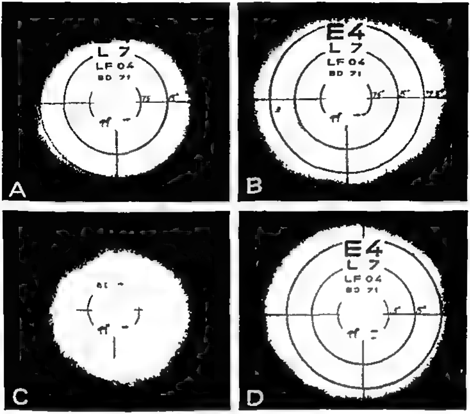

Fig 3
Examples of the pictures obtained with the cylinders No 5 No 3 No 8 and No 6 in Table 1

A Length 6 0 mm Diameter 2 1 mm
B Length 4 5 mm Diameter 3 1 mm
C Length 10 0 mm Diameter 2 1 mm
D Length 6 0 mm Diameter 3 1 mm

Examples of the results which could be obtained are shown in Fig 3 The 4 5 mm cylinder with diameter 3 1 mm and a concave posterior surface gave the sharpest pictures Also the corresponding cylinder of diameter 2 1 mm gave pictures of good sharpness With the longer cylinders and with the smaller diameters the blurring of the margins of the image field was marked It may be concluded that the cylinders of lengths up to 6 0 mm and diameters not less than 2 1 mm had an acceptable power of resolution

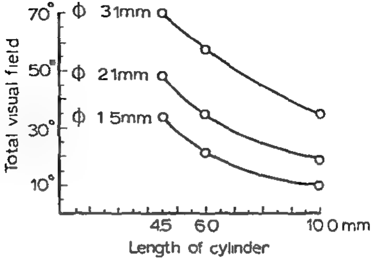

Fig 4

Visual fields obtained with 9 optical cylinders of different lengths and diameters 1 5 2 1 and 3 1 mm Cylinders Nos 1-9 in Table I

The visual fields which were obtained with different diameters and lengths of the optical cylinders may be seen in Table I and Fig 4 With the 4.5 mm long and 3 1 mm diameter cylinder with a concave posterior surface a circular visual field of approx 35° in all directions from the center was obtained i e a total visual field of 70° Even the 4 5 mm cylinder with diameter 2 1 mm gave a visual field of 48° None of the optical cylinders with length 10 mm gave a total visual field greater than 35°

The diameter of the "retinal image" field also depends on the length and the diameter of the optical cylinder (Table I) With the cylinder of length 4 5 mm diameter 2 1 mm and a concave posterior surface with a radius of curvature of 6 8 mm (No 2) the diameter of the image field was 19 mm With the corresponding cylinder of length 10 0 mm (No 8) the diameter was only 7 mm The diameter of the image fields with the biconvex and the planovex cylinders were somewhat smaller than what was obtained with the convex concave cylinder of the same length and diameter

The magnification is about the same with all the cylinders with a concave posterior surface used in these experiments The retinal images are 19 20% larger than that of the normal emmetropic eye whereas the magnification in an aphakic eye corrected with a spectacle lens of + 10 0 D is about 22% The

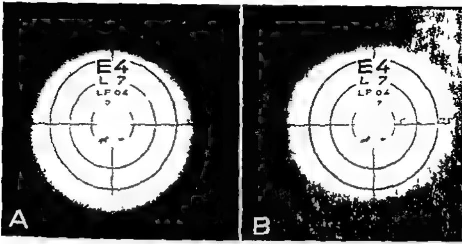

Fig 5

Pictures taken with an optical cylinder of length 4 5 mm and diameter ? 1 mm
A Untreated cylinder B Side of the cylinder painted black

biconvex (No 10) and the planoconvex (No 11) cylinders had smaller magnifi cation (Table I)

By photographing a series of surfaces of different shades of grey the relative aperture of the different optical cylinders could be compared As expected it was found that the thick and short cylinders transmitted more light than the thin and long On comparing of a 4 5 mm cylinder of diameter 2 1 mm with an optical system of known aperture ratio revealed that an exposure time for the cylinder of 1/50 of a second gives grey shades corresponding to the shades obtained using an optical standard system with shutter 5 6–11 at 1/250 seconds This means that this cylinder has an aperture ratio of 1 11–1 16 The theoretical value is 1 12 86

In our experiments we have placed the optical cylinders in the camera with a frontal free part, 2 mm long similar to the usual way of placing a kerato prosthesis in an actual eye (Figs 1 and 2) In this arrangement optical cylinders with a transparent polished side gave a sharp central picture with a somewhat blurred periphery surrounded by a zone of exposed film where no imaging could be seen (Fig 5 A)

Frosting the side of the cylinders improved the peripheral part of the pictures only to a small degree However when the side of the cylinders were painted black the sharpness and contrast of the whole picture and especial

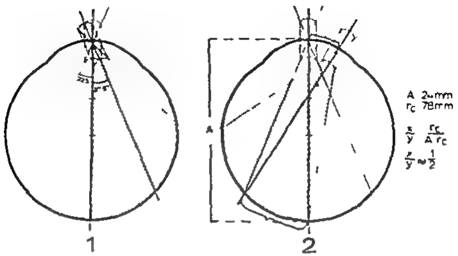

Fig 6

Diagrams showing position of lightstimulated retinal area

1 Cylinder out of alignment with the optical axis

2 Off center position of the cylinder

of the peripheral part improved considerably and at the same time made the zone of exposed film peripheral to the picture to disappear (Fig 5 B)

Unevenness of the corneal surface or uneven pressure of the different parts of the supporting tissues may cause the optical cylinder to get out of alignment with the optical axis of the eye although the cylinder may be correctly placed in the centre of the cornea This means that the centre of the retinal image will fall outside the macular area (Fig 6) If the angle between the axis of the cylinder and the optical axis of the eye exceeds half of the cylinder's total visual angle the whole retinal image will fall outside the macular area A 4 5 mm cylinder with diameter 2 1 mm must therefore lie at an angle greater than 24 to the optical axis to bring the whole picture outside the macula

As the anterior part of eyes operated on by prosthokeratoplasty may be so greatly deformed that it is difficult to identify the centre of the cornea improper positioning of the optical cylinder may also occur by placing the cylinder off centre in the cornea (Fig 6) As the radius of curvature of the anterior corneal surface is less than half the eye's axial length the centre of the retinal image field in such a case will fall more than twice as far from the macula as the distance of the cylinder axis from the cornea's optical

centre With a 4 5 mm cylinder of diameter 2 1 mm in which the diameter of the retinal image was about 19 mm the cylinder would therefore have to be placed about 4 75 mm from the cornea s optical centre for the whole retinal image to fall outside the macular area

An optical cylinder with flat end surfaces (No 12) gave no definable image on the film by itself even though the diameter was only 2 1 mm When a biconvex lens of +20 D was placed approx 30 mm in front of the cylinder a sharp image was obtained With this arrangement the magnification of the retinal image in relation to the normal phakic eye is about 190 % The diameter of the retinal image field was however only 12 mm and the extent of the total visual field 12° as compared to the 19 mm and 48° obtained with a cylinder of similar length with refracting surfaces

Although an optical cylinder with flat surfaces could not be used alone the pinhole effect of cylinders of such small diameters as these ones is obvious as the focal depth is very great A newspaper photographed both at 1 m and 1/3 m distance showed equally good resolution of the print (Fig 7) although the distance between the cylinder and the film remained unchanged Nor did displacing the optical cylinder 2 mm forward or backward relative to the film cause noticeable change in the clarity of the pictures

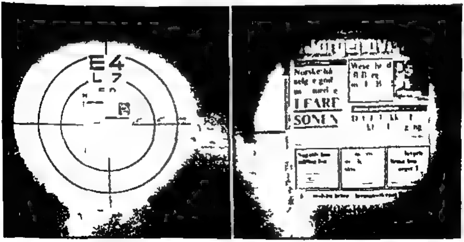

Fig 7

Newspaper photographed at d stances 1 m and 1/3 m Camera setting ∞ Cylinder No 2

Comments

In our experiments a straight film plane has been used to represent the spherical retina of the aphakic eye The blurring of the most peripheral part of the images due to this arrangement and differences in image sizes are considered of minor importance In all essentials the experiments give valuable guidelines when selecting parameters of the optical cylinders to be used in patients

The properties of optical cylinders of the same lengths and with the same radii of curvatures of the posterior surfaces as the ones used in the experiments but with radii of curvatures of the anterior surfaces calculated for use in aphakic eyes are summarized in Table II (Nos 1–11) In addition 2 cylinders with flat posterior surfaces and convex anterior surfaces (A B) and 3 cylinders with flat anterior and convex posterior surfaces have been tabulated (C, D E) The optical cylinders with concave posterior surfaces have the greatest magnification about 19 % a little less than the magnification in an aphakic eye corrected with a spectacle lens of +10 D A magnification of this order must be considered an adventage in most of the keratoprosthesis patients as their retinal function is often impaired

The lengths and diameters of the optical cylinders are the most important factors influencing the extent of the visual fields in patients with keratoprostheses In our experiments a 4 5 mm optical cylinder with diameter 2 1 mm reproduced a screen area representing a total visual field of 48° With an optical cylinder of 4 5 mm considered the shortest possible for use in patients, this means that it must have a diameter of at least 2 0 mm to obtain a visual field of more than 40° If a length of the cylinder of 10 mm is desired which may be the case in a patient with a heavely deformed anterior portion of the eye the diameter must be increased to about 3 0 mm to obtain a visual field of a similar magnitude

The extent of the visual field also depends on the curvature of the anterior surface of the cylinder The visual field widen with increasing radius of curvature of the anterior surface The greatest visual field can be obtained with a cylinder with a flat anterior surface. This would demand that all the refractive power of the cylinder should be located to the posterior surface which would have a convex form Such a cylinder with a diameter of 2 1 mm and a length of 4 5 mm would give a visual field about 10° greater than a cylinder of the same length with a posterior radius of curvature similar to the cornea (Table II) Instead of a magnification of about 19 % with the last mentioned cylinder the retinal image with the planoconvex cylinder would be about 6 % smaller than in the normal phakic eye

Table II

Properties of optical cylinders for implantation in aphakic eyes and the *calculated* magnification visual fields and retinal image fields

Cylinder No	Length mm	r_1 mm	r mm	Refractive power in diopters		Magnific per cent in eye	Visual field in degrees			Diameter of retinal image field in mm		
				in air	in eye		Φ1.5 mm	Φ2.1 mm	Φ3.1 mm	Φ1.5 mm	Φ2.1 mm	Φ3.1 mm
1–3	4.5	7.76	6.80	10.1	49.5	19.5	49.5	67.4	93.3	18.5	26.5	49.4
4–6	6.0	7.45	6.50	19.8	49.1	19.4	36.9	49.5	70.4	18.4	19.0	29.3
7–9	10.0	7.90	6.90	19.9	48.6	20.3	20.1	27.9	40.3	7.3	10.3	15.5
10	6.0	11.50	−10.00	33.2	55.4	5.9	38.4	52.9	75.4	12.4	16.9	25.8
A	4.5	9.37	∞	52.3	52.3	17.1	51.0	69.6	97.2	17.7	25.1	38.2
11	6.0	9.31	∞	52.6	52.6	11.4	37.5	51.6	73.3	12.7	18.0	26.9
B	10.0	9.16	∞	53.5	53.5	9.6	20.8	29.9	44.9	6.9	9.6	14.8
C	4.5	∞	−9.48	197.6	62.1	[illegible]	56.2	75.1	115.4	15.9	23.1	32.2
D	6.0	∞	−2.81	212.1	66.7	−19.0	42.4	59.0	86.3	11.1	15.4	27.3
E	10.0	∞	−1.84	266.3	83.7	−29.9	25.5	35.7	52.8	5.3	7.2	9.5

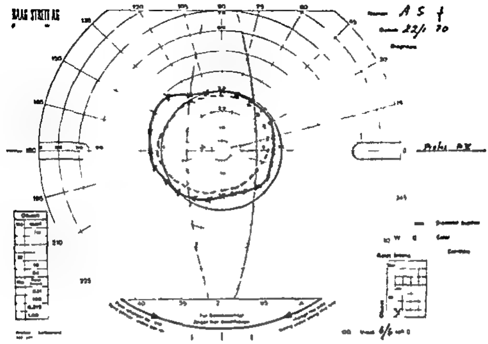

Fig. 8
The visual field of a patient with a keratoprosthesis. Length of the optical cylinder 4.5 mm, diameter 2.1 mm.

The extent of the visual field and the diameter of the retinal image fields obtained in our experiments (Table I and Fig. 4) are considerably smaller than the calculated values for similar cylinders intended for use in aphakic eyes (Table II). The poor illumination of the peripheral part of the retinal image field obtained with the optical cylinders is supposed to be the main cause of this discrepancy. The experience that keratoprosthesis patients with excellent visual function under favourable light conditions may have great visual difficulties in dim light is in full accordance with this. A scatter effect of reflected light coming in through the side of the anterior projection may also be of some significance. Our trials have shown that making the side of the optical cylinders black will improve the quality of the retinal image.

The diameter of the retinal image field also varies with the lengths and the diameters of the optical cylinders. In addition the shape of the posterior surface of the cylinder has some influence. A concave surface as used in our trials gives a larger image field than a flat or a convex one. With a concave posterior surface with a radius of curvature of 6.8 mm in cylinders of lengths

up to 6 0 mm and diameters not less than 2 1 mm the diameter of the retinal image fields is at least about 14 mm By using such cylinders in patients an accidental obliquity of the optical cylinder of more than about 1 ° in relation to the optical axis of the eye or an off center implantation on the cornea of more than 3 mm would be needed to place the whole image field outside the macula With longer and thinner optical cylinders the possibility of undesired projection of the whole retinal image field outside the macula increases

In eyes with known disease of the central retina a planned off center corneal implantation of the optical cylinder may be used to direct the image field to a functioning part of the retina

By combining a non refractive cylinder or a cylinder with reduced refractive power with a strong plus spectacle lens a maximum magnification of about 190 % may be obtained The visual field will however be restricted and the diameter of the image field smaller than with a cylinder with a concave posterior surface

Such low refracting cylinders may have their use in patients where a great magnification rather than a wide visual field is desirable for instance in patients with macular degeneration

In choosing an optical cylinder for a patient the length must first be decided Supposing that the combined thickness of the cornea the flange and the supporting tissues is at least 2.5 mm (Fig 1) and that there should be anterior and posterior projections of 1 mm to prevent overgrowth a 4 5 mm cylinder is the shortest possible for practical use The diameter of the cylinder should be 2 0–2.5 mm in order to give a sufficient visual field i e more than 40° A cylinder of length greater than 6 0 mm will rarely be necessary In such cases a diameter of 2 5–3 0 mm should be chosen to provide an adequate power of resolution and a visual field of more than 40°

We feel that optical cylinders with a posterior curvature like the normal cornea give the best combination of magnification visual field and diameter of the retinal image field to satisfy the demands in most keratoprosthesis patients We also think that a concave posterior surface may be a better protection against overgrowth of the surrounding tissues than a flat or a convex one The eye bulbs in patients requiring keratoprosthesis operations may be heavely deformed due to the pathological processes which have led to blindness and due to former surgical efforts Even though the optical cylinders have a great focal depth the possibility of deformation should be taken account of by ultrasonic measurement of the axial length of the eye in each individual case before defining the final design of the cylinder The radius of curvature of the anterior surface can hence be calculated to make the eye emmetropic after the operation

References

Pettersen T. E. & Sovereen K. ([illegible]) Experience with keratoprosthesis. Acta ophthal. [illegible]

Cardona H. ([illegible]) Keratoprosthesis. Acrylic optical cylinder with supporting intralamellar plate. Amer. J. Ophthal. [illegible]

Cardona H. ([illegible]) Mushroom transcorneal keratoprosthesis (Bolt and nut). Amer. J. Ophthal. [illegible]

Choyce D. P. ([illegible]) Perforating keratoprosthesis. The Choyce Mk II [illegible] piece perforating keratoprosthesis. Trans. Ophthal. Soc. U.K. [illegible]

Girard L. J., Moore C. D., Soper J. W. & O'Farrell W. ([illegible]) Prosthetic osteokeratoplasty [illegible] of a keratoprosthesis using full thickness ocular sclera and [illegible] al flap. Trans. Amer. Acad. Ophth. Otolaryng. [illegible]

Höfer H. ([illegible]) Erste Erfahrungen mit Kunststoff-Hornhautimplantaten. Klin. Mbl. Augenheilk. [illegible]

[illegible] O. E. ([illegible]) Kunststoffkeratoplastik (cornea artificialis). Vergangenheit und Gegenwart. Wien. klin. med. Wschr. [illegible] 1113-11[illegible]

Strampelli B. ([illegible]) Osteo-odontocheratoprotesi. Ann. Ottal. [illegible] 1039-1044

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A TECHNICAL IMPROVEMENT OF THE HAAG STREIT PACHOMETER

Short Communication

BY

NIELS EHLERS and STEFFEN SPERLING

Key words pachometry – corneal thickness – measuring accuracy

In recent years the interest in corneal thickness has been increasing mainly due to the appearance of the attachment I to the Haag Streit slit lamp which allowed the thickness to be measured with reasonable accuracy and speed The principle underlying this instrument is a measurement of the apparent thickness as seen at an angle of 40° Central localization on the cornea is secured by requesting the patient to look directly into the slit beam The thickness is thus measured along the line of sight which is not necessarily perpendicular to the anterior corneal surface

While the posterior corneal surface is probably rather spherical the expanding intraocular pressure tending to produce this shape the anterior surface is more paraboloid in accordance with an increasing thickness towards the periphery As it cannot be assumed that the anterior and posterior surfaces are exactly concentric the central corneal thickness has no unequivocal meaning Therefore it cannot be considered erroneous to measure the thickness along the line of sight However this gives rise to a systematic right left difference (left > right) increasing with the angle kappa between the line of sight and the line perpendicular to the anterior corneal surface and passing through the centre of the pupil (Ehlers & Kruse Hansen 1971) This difference is hardly

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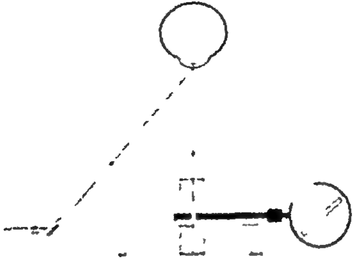

Fig. 1

Measurement of corneal thickness. The light from the left is reflected [illegible] corneal surface. When the light is seen in the microscope at the anterior edge of the slit image of the cornea the axis of the [illegible] and reflection are [illegible] and the beam falls perpendicular to the anterior corneal surface.

likely to represent a real difference between the two eyes. It disappears when the measurement is made along a line perpendicular to the anterior corneal surface (Ehlers 1974), which, for this reason, would seem to be a better measure for the central corneal thickness.

A simple way of securing a perpendicular incidence of the light was presented by Mishima & Hedbys (1968). Their principle should be understandable from Fig. 1. The only objection is their suggested reconstruction of the pachometer. We find it useful, therefore, to present our simple and cheap modification of the attachment to the Haag-Streit slit lamp.

Technical description. Three sheets of black perspex, bolted and glued together, slide over the pachometer arm without obstructing the path of the slit beam (Fig. 2). Two small 6 volts pin lights are mounted in holes drilled through the free end of the body. The lights are fed from the slit lamp power supply through a spring-balanced microswitch placed on the table of the slit lamp. The horizontal distance from the pin lights to the centre of the slit beam should be equal to the distance from the slit beam to the axis of the rotatable glass plate in the pachometer. When the pin lights are seen in the microscope

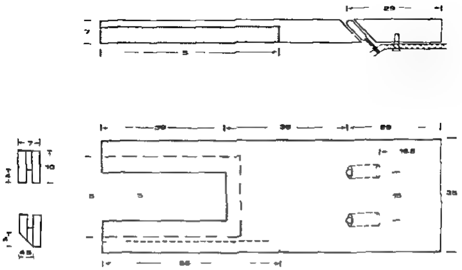

Fig 2
Diagram of the perspex apparatus to slide over the pachometer arm seen from below from the end and from the patients side All figures are in millimeters

at the anterior corneal surface the angle of incidence equals the angle of reflection and the slit beam is perpendicular to the anterior corneal surface (Fig 1) The use of two pin lights seen equidistanct from the horizontal dividing line of the visual field secures a perpendicular incidence also in the vertical plane

Comments The pachometer supplied by Haag Streit gives rise to a systematic right left difference which can be eliminated by measuring along a line perpendicular to the anterior corneal surface This latter measure may therefore be considered to be the better of the two The right left difference is probably due to the angle kappa von Bahr (1948) using a light incident from the right side of the microscope found that the right cornea was thicker than the left Moreover when a person is measured in the supine position with the head hanging the right cornea is found to be thicker than the left

The pin lights should be switched on only for the purpose of defining the measuring position as the alignment is made more accurate on a dark background The modification of the pachometer gives an increased measuring accuracy and it allows measurement of corneal grafts of peripheral thickness and of animal corneas

References

von Bahr G. ([illegible]) Measurements of the thickness of the cornea. *Acta ophthal. (Kbh.)* [illegible]
Ehlers N. ([illegible]) Graft thickness after penetrating keratoplasty. *Acta ophthal. (Kbh.)* [illegible]
Ehlers N. & Kruse Hansen F. ([illegible]) On the optical measurement of corneal thickness. *Acta ophthal. (Kbh.)* [illegible]
Mishima S. & Hedbys B. O. (1968) Measurement of corneal thickness with the Haag-Streit pachometer. *Arch. Ophthal. (Chicago)* [illegible] 710–713.

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SENILE CATARACT

Account of Cataract Extractions Performed in an Urbanized Population During the Third Quarter of the Present Century

BY

P BRÆNDSTRUP

Since the late 1940 s the annual number of cataract extractions performed at the Eye Department of the Municipal Hospital of Copenhagen has quintupled This increase has been followed by a tendency towards stabilisation An increase of the potential cataract clientele by about 60 per cent and an extended indication for operation are considered obvious causes of this rise to which must be added an increase inducing factor due to the popularisation of a visual rehabilitating operation in a community with a relative preponderance of old inhabitants
An attempt at a statistical calculation of the percentage of the population subjected to cataract extraction in a defined area related to age is presented This calculation may be of some guidance in the planning of ophthalmosurgical facilities

Key words cataract senile frequency of operation – surgery – gerontology – population urbanized

Since the late 1940 s the annual number of cataract extractions performed at the Eye Department of the Municipal Hospital of Copenhagen has shown a remarkable rise This rise has mainly comprised genuine senile cataracts but

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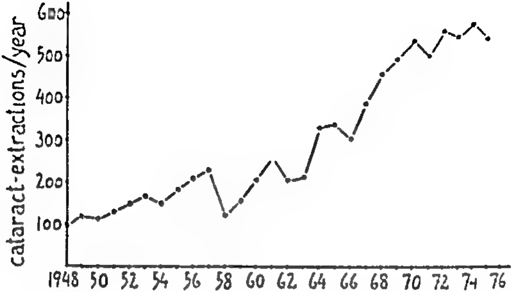

Fig. 1
Senile cataract. Number of cataract extractions/year in the Eye Department, the Municipal Hospital of Copenhagen, Denmark 1948–1975.

has also included complicated cataracts. However, during the past few years there has been a tendency towards stabilisation at this raised level (Fig. 1).

The characteristics of the curve presented in Fig. 1 reflect an obviously altered management of genuine senile cataract. This inspired an evaluation of the factors involved by the author, an ophthalmic surgeon who has experienced this notable evolution at first hand. Finally an attempt will be made to present a statistical calculation of the percentage of the population subjected to cataract extraction in a defined area (in this case the City of Copenhagen, the capital of Denmark, with its increasing relative number of old citizens).

The citizens of Copenhagen with senile cataract will almost without exception all be operated on either at the Municipal Hospital of Copenhagen (Kommunehospitalet) or at the State Hospital (Rigshospitalet), which is also situated in Copenhagen. An account of the numbers of citizens of Copenhagen operated on at the State Hospital has been available and from this it could be ascertained that the actual rise in cataract extractions at the Municipal Hospital did not depend on a shift of cataract clientele from the State Hospital.

The following factors will be considered: cataract prevalence in the population, change of the underlying potential cataract clientele, and extended indication for cataract extraction.

Prevalence of Cataract

The population of Copenhagen is homogeneously Caucasian With the exception of an expected increase in the number of cataracts in diabetics ophthalmologists do not generally consider that there is any increase in the prevalence of cataract though nothing definite is known about this In Danish cataract patients Anthonisen found 8 per cent diabetics in 1936 and Norn found 10 per cent diabetics in 1967 The cataract prevalence in the population is considered as being unchanged in the following considerations

Underlying Potential Cataract Clientele

In 1950 the population of the City of Copenhagen had its culmination with 768 100 inhabitants This number has since been declining As far as part of the present evaluation is concerned the number was 764 400 in 1949 and 639 300 in 1969 During the same period the number of inhabitants aged 55 or older rose numerically and consequently rose even more so in percentage ≥ 60 years increased about 50 per cent ≥ 70 about 60 per cent and ≥ 80 by about 100 per cent Within the stated observation period we may reckon with a percentage rise in the potential cataract clientele of about 60 per cent (Fig 2)

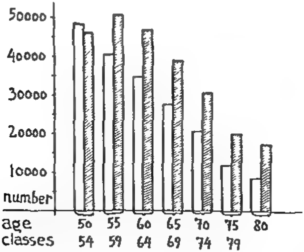

Fig 2

Senile cataract The population of the City of Copenhagen aged 50 years or older classified in five year age groups in 1949 (blank columns) and 1969 (hatched columns)

The rise in the number of older inhabitants has continued after 1969 (Table I). By New Year 19[illegible] the City of Copenhagen had [illegible]15 400 inhabitants of which 21.[illegible] per cent were [illegible] years old or older. The corresponding percentage for the remainder of the Danish population was 1[illegible]. (Total Danish population [illegible] 000 000.)

Such age determined population shifts are characteristic of the central areas of the larger cities with extensive suburbs which have been urbanized over the course of many years. However, the altered age distribution and the subsequent increase in potential cataract clientele cannot explain the rise in cataract extractions observed at the Municipal Hospital of Copenhagen.

Extended Indication for Cataract Extraction

An extended indication implies operation at an earlier stage of cataract development when there is less pronounced cataract induced visual impairment. This again depends on partly unforeseen technical improvements.

An account of the cases treated at the Municipal Hospital has concentrated on the visual acuity of the best eye on admission. Only those patients whose visual impairment was judged to be due to the cataract alone were regarded as being suitable for an estimation of an extended indication. Patients with unilateral cataract and admitted for operation on the second eye were not included. Furthermore, only those patients with a visual acuity in the best eye

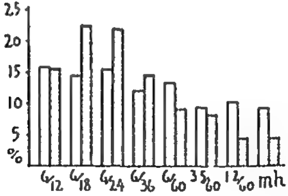

Fig. 3

Senile cataract. Visual acuity of best eye on admission for operation of the first eye in series from 1[illegible]–1[illegible]8, 19[illegible] and 1[illegible] 0 (blank columns) compared with series from 19[illegible] and 19[illegible] (hatched columns). Stated in percentage values. mh = movement of hand in front of eye.

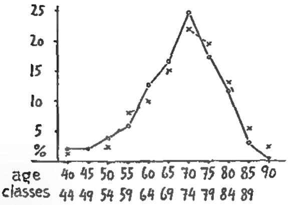

Fig 4

Senile cataract Age at operation of first eye in series from 1947 1948 1949 and 1950 (unbroken line) compared with series from 1969 and 1970 (broken line) Percentage presentation of five year age groups

of 6/12 or less were included Patients under 40 years of age at the time of operation were not included in the study

In this way selected consecutive series from 1947 1948 1949 and 1950 comprising a total of 270 patients were chosen for comparison with corresponding series from 1969 and 1970 with a total of 587 patients An extended indication can be confirmed and is shown in Fig 3 where percentage figures are stated for the visual impairment which motivated referral for cataract extraction in the two series

The age determined shift of the population caused a greater representation of elderly individuals in the late series while an extended indication implied operation at an earlier age The actual percentage age distribution at the time of operation in the two series is seen in Fig 4 There is no great difference between the two series the group aged 75 and older predominated slightly in the late series

Causes of Increased Number of Cataract Extractions at the Municipal Hospital of Copenhagen

An increase in the potential cataract clientele and an extended indication for operation are obvious factors for this The good results generally obtained will tend to popularise the operation and give rise to an increase inducing factor which in the author s opinion is of particular significance and worthy of a study

of its own. This is a matter of important social interest which not only concerns the ophthalmological profession but also generally involves the attitude of the population towards hospital admissions and surgery.

Number of Operations Related to Need for Treatment

As can be seen from Fig. 3 patients with a really disabling visual impairment are still being referred for cataract extraction. In the early series about 70 per cent had on admission a visual acuity of 2/60 or less, as compared with about 9 per cent in the late series. The early series included 25 patients admitted with dense bilateral cataracts. The duration of this condition is stated to have been less than twelve months in ten cases, 1–2 years in eight cases, and more than two years in four cases. The late series had 21 similar patients. Of these, eleven patients had been blind for less than twelve months, five patients for 1–2 years, and five patients for more than two years. Taking the increased number of annual operations into account, this implies that a patient blinded by cataract is seen about twice as often as was the case 25 years ago.

Unfortunately the case reports from the Municipal Hospital are not sufficiently detailed nor are they sufficiently homogeneous with regard to information concerning the social and mental states which accounted for the marked delays in cataract extraction. In Denmark access to ophthalmological service is principally easy and not financially straining. The possibility and the ability of the patient to make a decision concerning surgical treatment, regardless of whether they have lost their social independence or not, has been considered. Some patients together with their relatives or the group responsible for their welfare surely were not and still are not properly informed about the operation. Some patients on principal are against surgical interventions.

The numbers of "missed" cataract extractions in a population must be difficult to define. But it must be realised that even in an urbanized ophthalmologically well covered community there will exist citizens who need, but never show up for, proper surgical treatment.

It still appears important to point out to both the patients and to their close relatives that there is no age limit for cataract extraction. Moreover a description of the hospital stay also appears to be necessary. Among the nearest relatives of the patients the misapprehension still exists that cataract extraction, even when declared a success by the patient himself, involves an increased indication for referral to a nursing home.

Table I

Senile cataract Operations on first eye of inhabitants aged 40 years or older of the City of Copenhagen in 1969 1972 and 1973 Numbers of operations in five year age groups for each year and summarily for all three years and numbers of inhabitants in the corresponding age groups

Age classes	1969		1972		1973		Altogether	
	Operations	Population	Operations	Population	Operations	Population	Operations	Population
40–44	[illegible]	29 800	1	23 400	3	26 900	10	85 100
45–49	4	37 500	7	34 800	6	32 600	17	104 900
50–54	9	4[illegible] [illegible]00	15	47 500	12	40 600	36	125 800
55–59	28	46 200	17	45 200	31	43 400	76	134 800
60–64	49	47 000	31	46 900	44	46 100	124	140 000
65–69	69	39 000	87	39 700	70	39 900	226	118 600
70–74	100	30 500	106	31 600	93	31 900	299	94 000
75–79	77	20 000	82	21 900	110	27 400	269	64 300
80–84	60	11 300	74	19 300	60	19 600	194	36 200
85–89	28	4 900	27	5 300	41	5 500	[illegible]	15 700
90–	6	1 300	9	1 600	4	1 800	19	4 700
Total	436		456		474		1366	

Present Frequency of Operation for Senile Cataract on First Eye in the Population of the City of Copenhagen

The Copenhagen Statistical Office has calculated the incidence of cataract extraction in the first eye in the inhabitants of the City of Copenhagen aged 40 years and older who were operated on during the years 1969 1972 and 1973 Only those patients operated on at the Municipal Hospital and the State Hospital are included in these calculations The series have been divided into five year age groups (Table I) It appeared impossible to procure sufficient data for statistical calculations regarding operation on the second eye

To get an impression of a possible incidence rise since 1969 and knowing the

shifts in age group sizes, it was calculated how many patients would have been operated on in the first eye in the years 1972 and 1973 if the annual incidences of operation had remained the same as in 1969. The calculated figures are 4[illegible] and 4[illegible]0, the actual figures were 456 and 464. Thus the incidence of annual cataract extractions in the Copenhagen population shows signs of stabilisation at the present level (Table II).

The incidence of cataract extractions having been stable in recent years, it was considered relevant to proceed with a statistical calculation of the percentages of the citizens of the City of Copenhagen subjected to cataract extraction in at least one eye related to age. Fig. 5 reflects this calculation with its presuppositions mentioned in the figure text. I think that the curve, in spite of some reservations, could be of guidance for the organisation of ophthalmological surgical facilities. In the Municipal Hospital of Copenhagen now 55 per cent of cases admitted are cataract patients.

Table II

Senile cataract. Operations on first eye of inhabitants aged 40 years or older of the City of Copenhagen in 1969, 1972 and 1973. Incidences of operation for five year age groups calculated for each year and for three years together — on the basis of the figures in Table I.

Age classes	Observed annual incidences of operation			Calculated incidences of operation
	1969	1972	1973	
40–44	0.000[illegible]	0.0000	0.0001	0.0001
45–49	0.0001	0.000[illegible]	0.000[illegible]	0.000[illegible]
50–54	0.000[illegible]	0.0004	0.0003	0.0003
55–59	0.000[illegible]	0.0004	0.000[illegible]	0.000[illegible]
60–64	0.0010	0.000[illegible]	0.0010	0.0009
65–69	0.0018	0.00[illegible]	0.0018	0.0019
70–74	0.0033	0.0038	0.00[illegible]	0.003[illegible]
75–79	0.004[illegible]	0.003[illegible]	0.004[illegible]	0.004[illegible]
80–84	0.00[illegible]	0.00[illegible]0	0.0048	0.0054
85–89	0.00[illegible]	0.00[illegible]1	0.00[illegible]	0.00[illegible]
90–	0.004[illegible]	0.003[illegible]	0.00[illegible]	0.0040

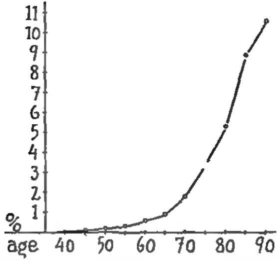

Fig 5

Calculated percentages of the population of the City of Copenhagen aged 40 years or older operated on for cataract of first eye in relation to age provided 1) the present annual incidence of operation persists 2) cataract patients whether operated on or not have the same mean expectation of life as that calculated statistically for the total population and 3) the new arrivals have had a chance of surgical treatment analogous to that of the original population Percentage values 40 years 0 % 45 0 06 % 50 0 14 % [illegible] 0 6 % 65 0 9 % 0 1 8 % 75 3 4 % 80 5 3 % 85 8 9 % and 90 10 6 %

Comments

Relevant surveys are sparse and not quite comparable to the present The survey presented by Caird Hutchinson & Pirie (1962) appears to be closest to the present one and in some respects is more detailed

In England and Wales the total number of cataract operations performed in hospitals in 1958 was 24 000 representing about [illegible] 000 patients in a population of 45 000 000 This implies a frequency of 0 00053 as informed by Sorsby (1962) In the same year the quoted frequency in Sweden was 0 00047 and for the Swedish population > 40 0 00108 (Halevi & Landau 1962) Caird Hutchinson & Pirie (1962) presented a detailed study of 690 cataract extractions in patients > 20 years of age carried out in the period 1957–62 in a defined English area with a total population of 195 193 The annual frequency is 0 00059 Sex age and preoperative vision of both eyes are considered A man of working age tends to be operated on when he has very poor vision in one

eye and good vision in the other. A woman regardless of age and older men tend not to be operated on until vision in both eyes is poor.

Considering the total population of the City of Copenhagen the frequencies were in 1949 0.0001988, in 1959 0.0003158, in 1969 0.000[illegible]8 and in 19[illegible] 0.000[illegible]9. It seems that in the City of Copenhagen as far as cataract extractions are concerned we were behind comparable countries and that a regulation has since taken place.

The popularisation of cataract extraction was mentioned as a significant increase inducing factor. In retrospect the retardation may partly have been caused by lack of proper information.

Retardation is an unevitable phenomenon which is difficult and sometimes dangerous to manipulate. In some respects retardation appears to be a community safeguard, in other respects against our welfare. Ophthalmologists have for many years considered the management of cataract to be sufficient and uncontroversial and our resources have mainly been converted to other fields, e.g. glaucoma and retinal detachment. The present study suggests that the management of cataract cases have in the past and still do have certain socio-ophthalmological aspects.

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The Copenhagen Statistical Office supplied information and calculations.
The case records of the State Hospital were kindly made available to me for the grouping of the inhabitants of the City of Copenhagen who had been operated on for senile cataract.

References

Anthonisen, H. (19[illegible]) The frequency of diabetic cataract and diabetic glaucoma as compared to the frequency of diabetes in the general population of Denmark. *Acta ophthal. (Kbh.)* *14*, 1[illegible]0-15[illegible].

Caird, F. I., Hutchinson, Mary & Little, Antoinette (19[illegible]) Cataract extraction in an English population. *Brit. J. prev. soc. Med.* *19*, [illegible]0-[illegible].

Halevy, H. S. & Landau, J. (19[illegible]) Hospitalized senile cataract in different Jewish communities in Israel. *Brit. J. Ophthal.* *4*[illegible], [illegible].

Norn, M. S. (19[illegible]) Diabetes mellitus and cataracta senilis. *Acta ophthal. (Kbh.)* *4*[illegible], 5[illegible]-5[illegible].

Sorsby, A. (19[illegible]) Cataract: some statistical and genetic aspects. *Exp. Eye Res.* *1*, [illegible].

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CAUSES OF ENUCLEATION FOLLOWING CATARACT SURGERY

BY

LAURI MERENMIES and AHTI TARKKANEN

Between the years 1969 and 1976 85 eyes which had undergone cataract surgery were accessioned to the Ophthalmic Pathology Laboratory of the Helsinki University Eye Hospital The specimens were submitted from the various eye departments of the country Of these 85 eyes nine had been enucleated within 9 months after surgery while in 64 cases the enucleation had been performed more than 12 months after surgery 40 eyes had had an attempted operation for senile cataract 30 eyes for traumatic cataract while the remaining cases were congenital cataract cases or cataracts in pre existing glaucomatous or chronic uveitis eyes Most frequent causes for the loss of the eyes were related to incomplete or abnormal healing of the operative wound such as epithelial down growth and closure of the chamber angle with extensive anterior synechiae leading to absolute glaucoma It is noteworthy that all cases of epithelial downgrowth were derived from the beginning of the observation period No new cases were obtained after 1969
Other important causes were purulent endophthalmitis and retinal detachment Haemosiderosis was a prominent cause in the group with traumatic cataract A careful histopathological analysis of eyes enucleated after cataract surgery is mandatory as it is from the complications we learn most in cataract surgery

Key words cataract surgery complications histopathological analysis – glaucoma absolute – endophthalmitis – epithelial downgrowth – haemosiderosis

Cataract extraction is the most often performed intraocular surgical procedure The results have improved with the years but occasional failures do occur Some of these may finally come to enucleation The careful evaluation by

histopathological study of the enucleated specimens is of great interest as in this way more information is obtainable than by clinical estimation alone.

There are relatively few studies reported in the literature of the causes of enucleation after cataract extraction. Blodi in 1962 reported on 31[illegible] such eyes. He confined his study to eyes which had had senile cataracts although he did include a few cases in which the operation had been a needling procedure or linear extraction. Schulze & Duke (19[illegible]) studied 100 most recently accessioned enucleated eyes in which an attempted intracapsular extraction of a senile cataract in an otherwise normal eye had been performed. In their study eyes with other types of surgical procedures for the removal of cataract were discarded. The purpose of the present study is to report the analysis of enucleated eyes accessioned to the Ophthalmic Pathology Laboratory of the Helsinki University Eye Hospital in 1962–197[illegible] in which cataract surgery had been attempted. Special attention was paid to the preoperative condition of the eye and to the time interval from surgery to enucleation.

Material and Methods

The material consists of 85 enucleated eyes which had undergone cataract surgery accessioned to the Ophthalmic Pathology Laboratory of the Helsinki University Eye Hospital between the years 1962 and 19[illegible]. The specimens were submitted from various eye departments of Finland. At the histopathological evaluation special emphasis was paid to the area of the surgical wound and possible remains of haemosiderin. Hence in addition to the haematoxylin and eosin and van Gieson stains numerous sections with periodic acid Schiff and iron stains were studied.

Results and Comments

The main underlying ocular conditions before cataract surgery as well as the time interval between cataract extraction and enucleation is shown in Table I. Of the 85 eyes 9 had been enucleated within 2 months after surgery while in most cases (in 64 out of 85) the enucleation had taken place more than 12 months after surgery.

1. Senile cataract (40 eyes)

The average age of the patients in this group was [illegible]1 years. In 26 eyes there had been an intracapsular and in 14 instances an extracapsular extraction.

Spontaneous choroidal haemorrhage is one of the dreaded complications and may occur once in the life time of an ocular surgeon Enucleation is usually necessary and this had been performed in 2 eyes of the material with senile cataracts

Purulent endophthalmitis had resulted to enucleation in [illegible] instances Most likely bacterial aetiology was responsible to the condition except in one instance in which a rhodotorula type fungus was cultured Fortunately as antibiotics and corticosteroids have become available an infection which is recognized early may be controlled A slip in aseptic technique is always a possibility

Chronic postoperative uveitis secondary glaucoma and phthisis had resulted to enucleation in altogether 20 instances It is noteworthy that in these eyes epithelial downgrowth had occurred in 6 eyes Fortunately no new cases had been accessioned after 1969 and this may be accounted to more meticulous wound closure as well as improvements in the surgical technique 7 eyes with secondary glaucoma showed closure of the chamber angle and anterior synechiae most likely due to defects in the mechanism of wound closure while retinal detachment was responsible for the loss of 6 eyes

Postoperative accidents had resulted to the loss of 5 eyes while in 2 eyes malignant melanoma of the choroid was visualized after cataract extraction

2 Cataract surgery in glaucomatous eyes (6 eyes)

In spite of the increased risks of cataract surgery in glaucomatous eyes only 6 eyes of this group were noted in the material One early enucleation was performed in an apparent case with malignant glaucoma while 5 eyes were lost later after surgery one due to purulent endophthalmitis through pre existing filtering bleb one due to epithelial downgrowth and three due to absolute glaucoma

3 Cataract surgery in eyes with pre existing chronic uveitis (5 eyes)

Surgical disturbance in eyes with chronic uveitis may lead to reactivation of the basic inflammatory condition Of the 5 eyes in this group 4 showed extensive cyclitic membranes while one eye was lost due to glaucoma and retinal detachment

4 Congenital cataract (4 eyes)

The most frequent postoperative complications of congenital cataract surgery are glaucoma pupillary occlusion and retinal detachment These were the causes also found in the present material of 4 cases Retained lens material may

Table I
Causes of enucleation and interval from cataract surgery to enucleation

Pre-existing condition	Causes of enucleation	Time interval (months)			Totals (eyes)
		0–2	2–12	over 12	
Senile cataract	Expulsive haemorrhage	2			2
	Purulent endophthalmitis				
	operative infection	2			2
	wound opening		1	2	3
	mycotic endophthalmitis		1		1
	corneal perforation			3	3
	Postoperative uveitis				
	epithelial downgrowth			2	2
	retinal detachment		1	1	2
	Secondary glaucoma absolute				
	closure of the chamber angle				
	epithelial downgrowth		1	2	3
	surgical aniridia			1	1
	thrombotic glaucoma			2	2
	Phthisis				
	choroidal and retinal detachment			2	2
	epithelial downgrowth retinal detachment		1		1
	Postoperative accident				
	opening of the surgical wound			3	3
	contusion injury	1		1	2
	Malignant melanoma of the choroid		1	1	2
	Retinal detachment suspicion of tumour		1		1
Cataract in eyes with pre-existing glaucoma	Malignant glaucoma (choroidal and retinal detachment)	1			1
	Glaucoma absolute				
	several operations			3	3
	epithelial downgrowth			1	1
	Purulent endophthalmitis through filtering bleb			1	1

(cont.)

Table I (contd)

Pre existing condition	Causes of enucleation	Time interval (months)			Totals (eyes)
		0–2	2–12	over 12	
Cataract in eyes with pre existing chronic uveitis	Uveitis cyclitic membranes			2	2
	Haemosiderosis			1	1
	Glaucoma absolute cyclitic membranes			1	1
	Glaucoma absolute retinal detachment			1	1
Congenital cataract	Glaucoma absolute chronic uveitis			1	1
	Haemosiderosis retinal detachment			2	2
	Phthisis chronic uveitis			1	1
Traumatic cataract	Haemophthalmos	2			2
	Keratectasis retinal detachment	1			1
	Purulent endophthalmitis		1		1
	Chronic uveitis choroidal and retinal detachment		4		4
	Haemosiderosis choroidal and/or retinal detachment		1	8	9
	Secondary glaucoma absolute closure of the chamber angle			5	5
	haemosiderosis			4	4
	Corneal dystrophy epithelial down growth			2	2
	Corneal perforation			1	1
	Postoperative accident			1	1
					85

lead to phakoanaphylactic inflammation and formation of cyclitic membranes. All these eyes were derived from the beginning of the observation period when occasional needling and linear extraction methods were still practiced. Since then, with the careful removal of the lens material by various suction methods no eyes have come to enucleation.

5. Traumatic cataract (30 eyes)

The prognosis of the eyes after surgery for traumatic cataract depends on the extent of the original injury. In this group of 30 cases 9 eyes were lost due to extensive haemosiderosis after intraocular bleedings leading to choroidal and/or retinal detachment. In 4 further cases haemosiderosis had resulted to absolute glaucoma due to extensive closure of the filtration angle leading to the loss of the eye.

In the papers of Blodi (19 ?) and Schulze & Duke (1964) it was reported that incomplete or abnormal healing of the operative wound was in many cases directly responsible for establishing the conditions which ultimately led to enucleation. Approximately one third of the eyes in the series of Schulze & Duke disclosed histological evidence of poor wound closure. In the present series the views of these authors are confirmed. In the series of 40 eyes enucleated following surgery for senile cataract 15 eyes showed evidence of poor wound closure with resultant epithelial downgrowth in 6 cases and closure of the chamber angle in 7 cases. A careful histopathological analysis of eyes enucleated following cataract surgery is mandatory as it is from the complication in cataract surgery we learn most (Hilding 19 2).

References

Blodi F. C. (19) Ursache und Häufigkeit der Enukleation nach Staraus ziehung. *Klin. Mbl. Augenheilk. 140*, 404–410.

Hilding A. C. (19 ?) The experimental approach to cataract surgery. *Amer. J. Ophthal.* 5 – 5 96.

Schulze R. R. & Duke J. R. (19) Causes of enucleations following cataract extraction. *Arch. Ophthal. (Chicago)* 3 4).

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ON THE MOLECULAR BIOLOGY OF THE VITREOUS IN THE APHAKIC EYE

BY

SVEN ÖSTERLIN

The vitreous of aphakic and phakic eyes was assayed for hyaluronic acid Intracapsular cataract extraction was regularly followed by decreased hyaluronic acid concentration and studies on the distribution of hyaluronic acid within the vitreous cavity showed that removal of the lens facilitates diffusion of hyaluronic acid into the anterior chamber Based on these studies certain postoperative features of the aphakic eye are discussed

The instability of the vitreous gel as reflected by rupture of the anterior vitreous face and an increased incidence of vitreous detachment supports the hypothesis of hyaluronic acid as a stabilizer of the gel The decreased adhesion of the neural retina in the aphakic eye might be caused by the loss of hyaluronic acid Normally the high concentration of hyaluronic acid adjacent to the retina contributes to the resistance of bulk flow of fluid into the subretinal space making it possible for the active transport system of the pigment epithelium to maintain a pressure drop across the neural retina

It is anticipated that saccades create currents in the fluid vitreous close to the eye wall after vitreous detachment Model experiments showed that these currents were greatly enhanced when the concentration of hyaluronic acid was lowered

Key words vitreous aphakic eye – vitreous hyaluronic acid – aphakia chorioretinal adhesion – vitreous hydrodynamics

lead to phakoanaphylactic inflammation and formation of cyclitic membranes. All these eyes were derived from the beginning of the observation period when occasional needling and linear extraction methods were still practiced. Since then, with the careful removal of the lens material by various suction methods no eyes have come to enucleation.

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In the papers of Blodi (1962) and Schulze & Duke (19[illegible]) it was reported that incomplete or abnormal healing of the operative wound was in many cases directly responsible for establishing the conditions which ultimately led to enucleation. Approximately one third of the eyes in the series of Schulze & Duke disclosed histological evidence of poor wound closure. In the present series the views of these authors are confirmed. In the series of 40 eyes enucleated following surgery for senile cataract 13 eyes showed evidence of poor wound closure with resultant epithelial downgrowth in 6 cases and closure of the chamber angle in 7 cases. A careful histopathological analysis of eyes enucleated following cataract surgery is mandatory as it is from the complication in cataract surgery we learn most (Hilding 1962).

References

Blodi, F. C. (19[illegible]) Ursache und Häufigkeit der Enukleation nach Starausziehung. *Klin. Mbl. Augenheilk.* 140: [illegible]04–[illegible]10.

Hilding, A. C. (19[illegible]) The experimental approach to cataract surgery. *Amer. J. Ophthal.* [illegible]

Schulze, R. R. & Duke, J. R. (196[illegible]) Causes of enucleations following cataract extraction. *Arch. Ophthal. (Chicag.)* [illegible]

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Table I

Hyaluronic acid concentration in the vitreous of phakic and aphakic eyes

Case No	Age (years)	Sex	Duration of aphakia (years)	Hyaluronic acid (μg/ml)	
				Phakic eye	Aphakic eye
1	[illegible]3	Male	2	164	4
[illegible]	92	Male	3	120	31
3	70	Female	4	365	190
4	86	Female	6	169	43
[illegible]	69	Female	6	41	14
6	96	Male	6	164	9
7	[illegible]4	Male	6	4[illegible]9	106
8	75	Male	9	[illegible]35	51
9	10[illegible]	Female	10	3[illegible]0	27
10	7[illegible]	Female	11	–	31
11	72	Male	13	[illegible]	43
12	96	Male	25	154	[illegible]5

(From Österlin Excerpta Medica International Congress Series 22[illegible] 1620 19[illegible]1)

Table II

Distribution of hyaluronic acid in the vitreous of aphakic eyes

Case No	Hyaluronic acid (μg/ml)	
	Peripheral region	Anterior region*
1	52 (1[illegible]6)	16 (144)
[illegible]	43 (190)	10 (96)
4	62 ([illegible]10)	[illegible]0 (130)
[illegible]	51 (210)	8 (117)
7	204 (430)	83 (3[illegible]4)
10	47 (121)	18 ([illegible]0)
1[illegible]	48 (178)	10 (156)

* Figures in parentheses represent the hyaluronic acid content in the corresponding phakic eye

(From Österlin Excerpta Medica International Congress Series [illegible] 16[illegible]0 19[illegible]1)

In 7 pairs of eyes the topographic distribution of hyaluronic acid was examined. The distribution pattern in phakic eyes is well known: the cortical layer contiguous to the retina contains the highest concentration of hyaluronic acid. The concentration gradually decreases towards the center of the vitreous and the region adjacent to the lens and posterior chamber (Table II). This distribution pattern has been interpreted as a diffusion gradient maintained by the production of hyaluronic acid in the cortical tissue layer and the escape of the hyaluronic acid molecules at the anterior vitreous surface (Østerlin & Balazs 1968). The distribution in the aphakic eye is very similar to the gradient present in the phakic eye (Table II). The gradient is probably maintained by the same mechanism. In the phakic eye the great difference between hyaluronic acid concentration in the aqueous and vitreous indicates that the fibrillar network of the vitreous and especially the cortical tissue layer forms a considerable diffusion barrier. In addition the area available for escape is limited by the lens.

The much steeper gradient in the aphakic eyes and the low concentration of hyaluronic acid in the anterior vitreous suggest that the escape of hyaluronic acid is facilitated in the aphakic eyes most probably by the increased area available for passage of hyaluronic acid molecules into the aqueous.

The series of events following removal of the lens could be summarized as follows. In the phakic eye the normal collagen network is supported by hyaluronic acid whereas in the aphakic eye the hyaluronic acid disappears in larger amounts than normally. When this type of vitreous is exposed to mechanical stress it collapses with the formation of liquid pools. Simultaneously the collagen filaments may aggregate to large fibrils resulting in partial constriction of the network. Initially the changes are taking place on the molecular level but will later appear as clinically recognizable changes.

The loss of hyaluronic acid after removal of the lens may not only influence the stability of the gel but could also be a factor explaining the weak retinal adhesion in the aphakic eye. The following discussion on retinal adhesion will be based on the physical properties of hyaluronic acid *in vitro* and the suggested mechanisms should be considered as hypothetical models rather than established knowledge.

In the phakic eye retinal apposition is maintained by a series of small forces partly mechanical and partly dynamic (Zauberman & de Guillebon 1972). A concept has slowly been accepted that at least part of the dynamic force is dependant upon the transport of fluid and macromolecules from the subretinal space and the maintainance of a small pressure drop across the retina (Fatt & Shantinath 1971). The mechanism has been illustrated using the tube type tire as a model (Fig. 1). The nural retina is the inner tube and is pressed against

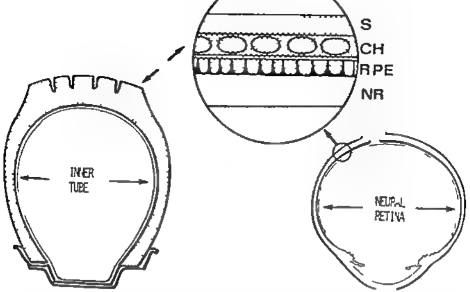

Fig 1

Retinal apposition is explained using the tube type tire (left) as a model The neural retina (NR) is the inner tube and is pressed against the casing corresponding to the retinal pigment epithelium (RPE) the choroid (CH) and the sclera (S) (stippled areas) by the internal pressure Pressure drop across the retina 0 52 x 10 3 mmHg (Fatt & Shantinath 1971)

the casing the retinal pigment epithelium the choroid and the sclera by the internal pressure (note *not* the solid vitreous liquefaction of the vitreous does not lead directly to vitreous detachment)

The model requires that the retina be impermeable to the internal fluid One can easily visualize that an inner tube of cheese cloth would not be pressed against the inner side of the tire casing We know however that the imper meability is only relative and that normal retina is permeable to fluid and even relatively large molecules such as proteins e g peroxidase will move from the vitreous to the subretinal space in less than 20 minutes (Peyman & Bok 1972)

Even though the neural retina and its inner limiting lamina offer a consider able resistance to flow one shall not forget the layer of hyaluronic acid present in high concentration adjacent to the basal lamina On the molecular level this layer can be visualized as a very fine network of polysaccharide chains trapped

within a much coarser network of collagen fibrils (Balazs 1965) (Fig. 2 A). Polysaccharides in concentrations present in the vitreoretinal zone offer considerable resistance to water flow (Ogston 1970) and for obvious reasons much higher resistence than the collagen network. Of importance is also the fact that hyaluronic is still present even if the collagen network is missing in the vitreoretinal zone as in vitreous detachment (Foos 1975, Osterlin 1976). In the aging eye with degenerative changes causing ruptures in the basal lamina or even absence of this structure and thinning of the retina (Foos 1972, Gartner 1971

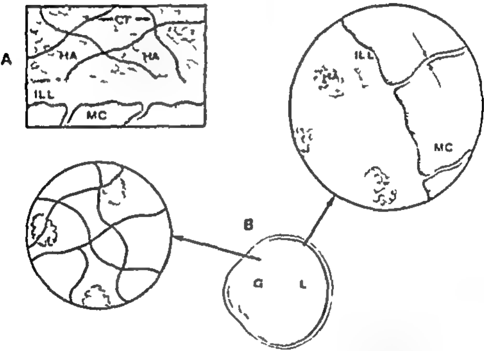

Fig. 2 A

Organisation on the molecular and ultrastructural level of the vitreoretinal border in the phakic eye. *The hyaluronic acid chains (HA) form a continuous threedimensional* network within the coarser network of collagen filaments (CF). Inner limiting lamina (ILL). Muller cells (MC).

Fig. 2 B

Vitreous in the aphakic eye. Liquid vitreous (L). Vitreous gel (G). Single hyaluronic acid molecules will not resist the bulk flow of liquid. In the peripheral vitreous (right) the decreased resistance to flow will make the forces maintaining retinal *adhesion in*efficient, especially in case of defects in the inner limiting lamina, when there is free communication between the vitreous cavity and the intercellular spaces of the retina *(arrows).* The motility of the vitreous gel (left) is increased when no hyaluronic acid is occupying the meshes in the collagen network.

Straatsma et al 1974) the hyaluronic acid network is of special importance by very effectively blocking small retinal defects and increasing the resistence to flow

The insidious loss of the hyaluronic acid from the vitreous in the aphakic eye (Österlin 1971 Henricsson & Österlin 1976) makes the retina - the inner tube leaky and consequently retinal adhesion weaker (Fig 2 B) Small retinal defects cause a retinal detachment and in case of larger holes or tears the tendency to demarcation has been lost as reflected in the low incidence of subclinical detachment or detachment limited to one quadrant in the aphakic eye (Ashrafzadeh et al 1973)

A decrease in the hyaluronic acid concentration will also change the hydrodynamic pattern within the vitreous cavity In the majority of the aphakic eyes the vitreous gel has collapsed and is located in the anterior and inferior part of the cavity while the remaining space is filled with liquid vitreous The gel will sooner or later loose its content of hyaluronic acid the finer component in the double network of the vitreous and also its main resistence to bulk flow of water which means that the movements of the gel in the liquid filled space is facilitated This mechanism could explain the abnormal motility of the vitreous gel in the aphakic eye (Fig 2 B)

The hydrodynamic events in the posterior liquid pocket of the vitreous cavity have been the subject of recent investigations (Rosengren & Österlin 1976) Model experiments showed that currents elicited by rotatory movements of a small liquid filled vessel were able to elevate a perforated membrane covering the inner surface of the vessel The experiments did also show that the currents in the extreme periphery of the vessel were markedly subdued when the viscosity of the liquid was increased

The viscosity of the liquid vitreous is regulated by the concentration of hyaluronic acid and its molecular size Hyaluronate solutions exhibit interesting rheological properties (Ogston 1970) Due to the very high molecular weight and the open coil structure the polysaccharide has an extremely high intrinsic viscosity Furthermore due to intermolecular interaction like entanglement the viscosity is strongly concentration dependent In many of the aphakic eyes the hyaluronic acid concentration drops and the viscosity will approach zero values The effect of hyaluronate on the hydrodynamics in a small vessel was recorded on film (Österlin & Larsson 1976 unpublished) When the vessel was filled with a buffer containing lipid particles and rotated with fits and starts to and from like saccadic movements of the eye a marked displacement of the particles was obtained in a 2–3 mm thick layer of the extreme periphery If instead a 0 02 % buffered hyaluronate solution was used movements in the peripheral layer during saccadic rotation was negligible

Intracapsular cataract extraction is regularly followed by a decreased hyaluronic acid content in the vitreous. Based on this important change in the macromolecular composition an attempt has been made to explain certain postoperative features of the aphakic eye.

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References

Ashrafzadeh M. T., Schepens C. L., Elzeneiny I. I., Mostafa K., Morse L. & Kraushar M. F. ([illegible]) Aphakic and phakic retinal detachment. *Arch. Ophthal. (Chicago)* 89, 4[illegible]6–483.

Balazs E. A. ([illegible]) Physiology of the vitreous body. In Schepens C. L. Ed. *Importance of the vitreous body in retina surgery with special emphasis on reoperations* p. [illegible] C. V. Mosby Comp. New York N.Y.

Balazs E. A. ([illegible]) The molecular biology of the vitreous. In *New and controversial aspects of retinal detachment* p. [illegible] McPherson A. Ed. Hoeber Medical Division New York, Evanston and London.

Fatt I. & Shantinath K. ([illegible]) Flow conductivity of retina and its role in retinal adhesion. *Exp. Eye Res.* [illegible]

Foos R. Y. ([illegible]) Vitreoretinal juncture: topographical variations. *Invest. Ophthal.* 11 801–808.

Foos R. Y. ([illegible]) Ultrastructural features of posterior vitreous detachment. *Albrecht v. Graefes Arch. Klin. Exp. Ophthal.* [illegible] 103–111.

Gartner J. ([illegible]) The fine structure of vitreous base of the human eye and pathogenesis of pars planitis. *Amer. J. Ophthal.* [illegible] 131–137.

Henricsson M. & Osterlin S. Changes in the macromolecular composition of the vitreous after cataract extraction. A comparison between the intracapsular and extracapsular methods. (In preparation).

Jaffe N. S. & Light D. S. ([illegible]) Vitreous changes produced by cataract surgery. A study of [illegible] aphakic eyes. *Arch. Ophthal. (Chicago)* [illegible] 541–5[illegible]3.

Ogston A. G. ([illegible]) The biological functions of the glycosaminoglycans. In *Chemistry and Molecular Biology of the Intercellular Matrix* Vol. 3. Balazs E. A. Ed. Acad. Press London New York.

Osterlin S. ([illegible]) Changes in the macromolecular composition of the vitreous after removal of the lens. *Pr.* [illegible] *Int. Ophthal. Congr. Mexico D.F. Int. Congr. Ser.* [illegible] Excerpta Medica Amsterdam.

Osterlin S. ([illegible]) Changes in the vitreous with age. *Trans. ophthal. Soc. U.K.* 95 [illegible]

Osterlin S. & Balazs E. A. (19[illegible]) Macromolecular composition and fine structure of the vitreous in the owl monkey. *Exp. Eye Res.* [illegible] 534 [illegible]

Peyman G. A. & Bok D. ([illegible]) Peroxidase diffusion in the normal and laser coagulated retina. *Invest. Ophthal.* 11 [illegible]

Rosengren B & Österlin S (1976) Hydrodynamic events in the vitreous space accompanying eye movements *Ophthalmologica* 173 513–524
Schweer G & Neuberger H (1961) Zum hyaluronsäuregehalt des menschlichen Glaskorpers *Ber dtsch ophthal Ges* 64 306–307
Straatsma B R Zeegen P D Foos R Y Feman S S & Shabo A L (1974) Lattice degeneration of the retina *Amer J Ophthal* 77 619–649
Zauberman H & de Guillebon H (1972) Retinal traction *in vivo* and postmortem *Arch Ophthal (Chicago)* 87 549–554

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FORMATION OF AFTER-CATARACT BY REGENERATION OF HUMAN AND RABBIT LENS EPITHELIUM IN TISSUE CULTURE

BY

PER P. FAGERHOLM and BO T. PHILIPSON

Regeneration of lens epithelium on the lens capsule was studied in tissue culture. The entire capsule with attached epithelium was taken from rabbit lenses and from human lenses with cataract.

Generally, the epithelium grew in a mono layer but multilayered masses of cells were also seen. Most lens fibers degenerated during the first days and formed spherical membrane enclosed vesicles containing cytoplasm but no nuclei. The lens fiber remnants together with regenerating epithelium created structures that were similar in many ways to the clinical appearance of after-cataract.

Key words: human lens – rabbit lens – lens epithelium – lens capsule – after-cataract – tissue culture.

Many ophthalmic surgeons currently favour extracapsular cataract extraction for patients of all age groups and not only for the young. The major disadvantage associated with the extracapsular lens extraction is the formation of after-cataract on the posterior capsule.

After-cataract has been studied clinically (Koy 19[illegible]) and experimentally

on rabbits (McDonald et al 1974) and is known to consist mainly of regenerating lens epithelium and degenerating lens fibers If there is a strong inflammatory response a fibrotic membrane might be formed due to exudation and growth of other cells

An advantageous way to study the mechanism of regeneration of lens epithelium ■ in the tissue culture medium Lens epithelium has been cultured separately (van Venrooij et al 1974a b) but to our knowledge no studies of the regeneration of lens epithelium from human lenses on the capsule have been undertaken In this study the technique and observations on the regeneration of epithelium from human lenses with cataract will be presented Rabbit lenses were used to test the method of cultivation and to give information on the behaviour of normal rabbit lens epithelium

Material and Methods

Nine human cataractous lenses and four rabbit lenses were used

The human lenses were obtained after intracapsular cataract extraction The lenses were extracted from patients whose ages ranged from 61 to 85 years they had senile cataract and were all very opaque The rabbits were killed with an overdose of Nembutal enucleated and the lenses were extracted with intact capsules

All lenses were dissected under an operating microscope in order to separate the major lens fiber mass from the capsule and epithelium The anterior capsule was cut from equator to equator in two directions with the intention of forming four triangular flaps of anterior capsule and epithelium These flaps attached to the posterior capsule were torn off the lens fiber mass and mounted in one piece on a cover slip using small drops of tissue adhesive (Cyanoacrylate B Braun Melsungen AG) The cover slip was then put into a Leighton tube (Bellco) and culture medium was added Each capsule preparation was cultured in a separate tube

The medium was composed of Eagles MEM with Earles salt solution containing 2 % calf serum inactivated at 56°C for 30 min Penicillium and streptomycin were added to the medium to make a final concentration of 100 IE/ml and 50 μg/ml respectively The pH of the culture medium was 7 4 The cultures were kept at 35°C and studied under a phase contrast microscope every day during the first week and every third day for the following six weeks The medium was changed every week in six of the human and two of the rabbit preparations while the others were left unchanged for methodological reasons

Fig. 4
Phase contrast micrograph of a small rabbit epithelial cell colony on the cover slip in the culture tube after 6 days of culture. (50 ×)

Two different kinds of epithelial regeneration were noted: 1) a monolayer of cells, 2) multilayered masses of cells. The monolayer was generally seen on the flat capsule, on both the anterior and posterior parts (Fig. 2). The multilayered lumps of cells were first and most frequently found at folds of the anterior capsule but were also later found on the flat surface (Fig. 3). On the cover slip and on the bottom of the tube an intense growth of epithelial cells was seen in groups forming a monolayer.

The epithelial cells from the human lenses with senile cataract behaved principally in the same way as the rabbit lens epithelium. In general, fewer lens fibers were attached to the capsular preparation and the capsular specimen was relatively transparent. Thus the epithelium was much easier to observe from the beginning of the tissue culture (Fig. 5). Groups of epithelial cells loosened from the capsule, as well as piles of lens fibers, during the first week

Fig 5

Phase contrast micrograph of epithelial cells from a human cataractous lens after 1 h of culture This phase contrast micrograph illustrates the good possibilities to observe the living cells when no lens fibers were attached 415 ×

when the capsule became even more transparent Lens fibers were always completely dissolved on the flat parts of the capsule following the same pattern of disintegration as in the rabbit preparation However the human lens fibers were more resistant and could remain for more than three weeks Growth of epithelial cells on the cover slip and on the bottom of the tube was seen but the rate of growth was much less intense as compared to those from rabbit Epithelial cells were growing on the capsule both in a monolayer and in multilayers Cells undergoing mitosis were occasionally seen On a flat capsular surface growth was mainly in a monolayer but on capsular folds epithelial cells grew in many layers often mixed with remaining lens fiber material (Fig 6)

Epithelial cell regeneration was seen in all but one of the preparations This preparation was derived from a human cataractous lens extracted from

Fig 6

Phase contrast micrograph of human lens epithelium after 3 weeks of tissue culture The cells are growing in multilayer within the fold of capsule to the left and in a mono layer on the posterior capsule to the right 90×

Fig

Micrograph of histologic section of a human lens capsule after 3 weeks in tissue culture The capsule is enclosing proliferating epithelial cells and amorphous masses of lens fibers remnants and material produced by the cells Haematoxylin eosin 100

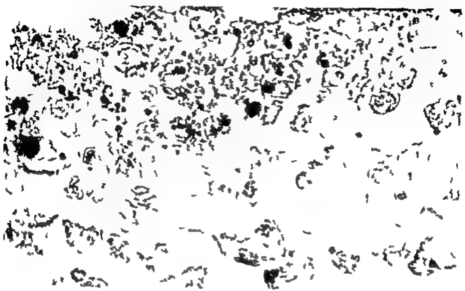

Fig 8
Higher magnification of similar structure as in Fig 7 Epithelial cells are mixed with extra cellular material 860 ×

a patient 84 years of age In this preparation the medium was changed every week Generally it seemed preferable to change the medium every week

Histological sections confirmed the *in vivo* findings (Fig 7) Proliferating cells remained at about their original size The cell shape became flatter when growing on a flat surface and seemed to have varying amounts of cytoplasm Dispersed cells appeared to contain more cytoplasm than those cells that were densely packed both in the mono and the multilayer In the cell clumps and on the capsule various amounts of extracellular material with fibrillar pattern were seen (Fig 8) The globular structures presumably formed by disintegrated lens fibers appeared to be encircled by a cell membrane and contained no nuclei or visible organelles

Discussion

Lens epithelium from rabbit and calf lenses has successfully been cultured for periods longer than a year (van der Veen & Heyen 1959 Shapiro et al 1969 van Venrooij et al 1974a b) The cells were either mechanically or enzymatically separated from the capsule or allowed to spread from the capsule over to the bottom of the culture flask.

In this study the capsule was deliberately placed directly in the culture

tube in order to study the regeneration of epithelial cells on it This kind of epithelium culture corresponds closely to the formation of after cataract in an eye without inflammation However the tissue culture medium used is different in composition from the aqueous humor In many respects the tissue culture medium can be made more favourable to the epithelial cells and more rapid growth can be expected than in the eye (Reddan et al 1970) In this study a low percentage of calf serum was used to avoid forcing cells into mitosis When the anterior capsule was stripped off islands of cells or single cells started to multiply Some cell colonies on the capsule might originate from cells detached from its original position and by movements in the culture medium reimplanted on a new place Loss of contact inhibition is probably the stimulus for cell growth (Shapiro et al 1969) This is also the case after minor lens injuries where regenerating lens epithelium also might heal the lens capsule (Young & Ocumpaugh 1966) The rabbit epithelial cells when regenerating in a clump are intermingled with amorphous substances probably produced by the cells Shapiro (1969) suggested that new collagen could be formed from lens epithelial cells in tissue culture A collagen like protein was also found to be produced by activated lens epithelial cells (van Venrooij et al 1974a)

Clinical and histological studies of after cataract in non inflamed eyes have shown that it mainly consists of remaining lens fibers and regenerating epithelium The after cataract can appear as a diffuse opaque membrane or may form structures known as Soemmering s ring or Elschnig pearls A typical Soemmering s ring is only seen when large masses of lens fibers remain between the anterior capsule flaps and the posterior capsule In these experiments only minor piles of lens fiber remnants were left under the folds of the anterior capsule However structures similar to Soemmering s ring but of much smaller size were seen in both the human and the rabbit specimens (Fig 8) Elschnig pearls (Elschnig 1911) are generally considered to consist of proliferation of epithelial cells in a mass Sometimes these cells contain large amounts of cytoplasm (Roy & Hanna 1975) In this restricted material cell masses observed were about as frequent on human as on rabbit lens capsules There appeared to be a variation in content of cytoplasm but no extremely large cells were seen However lens fiber remnants often created similar globular structures to those shown by Rafferty & Coossens (1975) on degenerating lens fibers after trauma to the lens Such structures may be hard to differentiate from epithelial cells by clinical slit lamp examination

Consequently this kind of tissue culture causes an epithelial regeneration creating changes on the posterior lens capsule similar to after cataract This model will be used in further studies of epithelial regeneration on the capsule and for studying the possibilities of preventing the formation of after cataract

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References

Elschnig A (1911) Klinisch anatomischer Beitrag zur Kenntnis des Nachstares *Klin Mbl Augenheilk 49* 444

McDonald J E Roy F H & Hanna C (19 4) After cataract of the Rabbit Autoradiography and Electron Microscopy *Ann Ophthal 6* 3

Rafferty N S & Goossens W (1975) Ultrastructural Studies of cataractogenesis Observations of a Repair Process in Mouse Lens *Amer J Anat 142* 177

Reddan J R Harding C V Unakar N J & Bell R M (1970) Electron Microscopy of cultured mamalian lenses I Initial changes which precede and accompany the stimulation of DNA synthesis and motosis *Invest Ophthalmol 9* 496

Roy F H (1971) After Cataract Clinical and pathological evaluation *Ann Ophthal 3* 1364

Roy F H & Hanna C (1975) After cataract In Bellows J B Ed *Cataract and Abnormalities of the Lens* 461–469 Grune & Stratton Inc 1975

Shapiro A L Siegel I M Scharff M [illegible] & Robbins E (1969) Characteristics of cultured lens epithelium *Invest Ophthalmol 8* 393

van Der Veen J & Heyen C F A (1959) Lens Cells of the Calf in Continuous Culture *Nature (Lond) 183* 1137

van Venrooij W J Groeneveld A A Bloemendal H & Benedetti E L (1974a) Cultured Calf Lens Epithelium I Methods of Cultivation and Characteristics of the Cultures *Exp Eye Res 18* 517

van Venrooij W J Groenveld A A Bloemendal H & Benedetti E L (1974b) Cultured Calf Lens Epithelium II The Effect of Dexamethasone *Exp Eye Res 18* 527

Young R W & Ocumpaugh D E (1966) Autoradiographic studies on the growth and development of the lens capsule in the rat *Invest Ophthalmol 5* 583

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RETINAL DETACHMENT IN APHAKIA

BY

STAFFAN STENKULA and RAGNAR TÖRNQUIST

In a prospective study five hundred consecutive cases of cataract operations were followed during ten years Nine cases of retinal detachment were observed
In a retrospective study [illegible] cases with aphakic retinal detachment were studied according to type of cataract operation interval between this operation and the onset of retinal detachment refraction area of detachment and results of treatment
About fifty percent of the cases of retinal detachment are observed during the first year after the cataract operation At the first examination the detached area is usually larger in aphakic eyes than in phakic eyes The anatomical and functional cure after detachment operation is probably less in aphakic than phakic eyes

Key words aphakia – retinal detachment

Retinal detachment (RD) occurring in aphakic eyes involve many pathogenetic and prognostic problems of great interest Most publications discussing the characteristic differences between aphakic (ARD) and phakic retinal detachments (PRD) are based on retrospective statistical analysis of clinical materials representing patients from undefined populations The materials tend to be biased as aphakic eyes with retinal detachment are thought to have a bad prognosis and are often referred to a specialized clinic The significance of different characteristics of ARD is probably best evaluated in a series representing all cases from a population area

Generally prospective studies give more consistent results It is difficult however to collect large series of patients operated on for cataract with a similar surgical technique and the number of ARD tends to be too small for statistical analysis

Material

Prospective study

Five hundred consecutive cases of cataract operations performed at the Eye Clinic of the Region Hospital in Örebro 1962–65 were followed during ten years The prevalent surgical technique during this period was intracapsular delivery with forceps (84 % against 16 % extracapsular extractions or needlings)

Nine cases of RD representing 1 8 % were observed Six cases occurred during the first four postoperative months and in the remaining three cases there were intervals of two to nine years between cataract surgery and the onset of RD

Extracapsular extraction had been performed in three of the nine cases of ARD In four eyes of ARD the operation was complicated by vitreous loss

Retrospective study

During the last 15 years many complicated cases of RD have been referred to the Eye Clinic in Örebro from all parts of Sweden During the same period all cases from a population area of 560 000 people (the counties of Varmland and Örebro) have been treated in this clinic This unselected group of patients (Group A) is the basis of the following statistics concerning differences between ARD and PRD

From 1961 to 1975 77 eyes with ARD were included in group A (Table I) In the same period 5001 cataract operations were performed in this population Thus the incidence of RD after cataract surgery was 1 5 % which is nearly the same figure as in the prospective study

The relative number of ARD in Group B (patients from other parts of Sweden and from foreign countries) was 14 3 % against 9 7 % in Group A Thus more cases of ARD are included in the selected group

In a few aphakic eyes only retinal degeneration and/or retinal tears without RD were observed this was much more common in the phakic eyes

The number of patients with ARD in Group A was 71 (31 males and 40 females) 47 patients had cataract surgery in only one eye but one of them had had a retinal detachment in the other phakic eye 24 patients were aphakic

Table I
Patients referred for retinal surgery 1961–1975. Number of eyes

Group	Aphakic eyes: without RD	Aphakic eyes: with RD	Aphakic eyes: total	Phakic eyes: without RD	Phakic eyes: with RD	Phakic eyes: total	Total
A	3	4	[illegible] (9.[illegible] %)	207	513	71[illegible] (90.[illegible] %)	[illegible]9 (100.0 %)
B		1[illegible]	1[illegible] (11.[illegible] %)	215	[illegible]4	[illegible] ([illegible] %)	11[illegible] (100.0 %)
Total	10	[illegible]	21[illegible]	430	1[illegible]	1[illegible]0	1919

Group A: Patients from the counties of Varmland and Orebro.
Group B: Patients from other counties of Sweden.
RD: Retinal detachment.

in both eyes, five of them had previously been treated for RD in the other eye. Bilateral RD was found in 12.5 % in an unselected series of patients (Tornquist 1961); in this group of ARD the relative number of bilateral cases was higher, 20.8 %, but the difference is not significant.

Results and discussion

The aphakic state seems to predispose to RD because the incidence in the total population is less than in the aphakic group. In a stable population the incidence rate of RD for people in the "cataract age" is 0.05–0.10 % (Bohringer 1956, Okun 1961) or 20–25 times less than in the ARD group.

All statistics confirm the importance of myopia as a predisposing factor in RD. Highly myopic eyes may, however, show a higher prevalence of cataract. Thus if a large proportion of aphakic eyes is myopic the predisposition for RD may be a consequence of the different distribution of refractive errors.

In retrospective studies the pre-cataract refraction is often uncertain. Selected clinical materials from retinal centers may include more highly myopic eyes also in the aphakic group. A very large proportion of myopes was included in the series of Kuben (1976) but Ashrafzadeh et al. (1973) found more myopes in the phakic group than in the aphakic one.

The ARD group from the unselected population in the present series did

Table II
Refraction Number of eyes Group A

Refraction/Phakic equivalent	Aphakic eyes	Phakic eyes	Prevalence in healthy young men (Stromberg 1936)
+2 25 or more hyperopia	[illegible]	5	
+2 00 to −2 00	56	409	
−2 25 to −5 00	12	89	
−5 25 to −10 00	4	6[illegible]	
−10 25 to −20 00	[illegible]	29	
More myopia than −20 00	1	8	
Unknown	2	61	
Total	[illegible]	[illegible]	
Myopia > −2 00	24 [illegible] %	29.5 %	2 9 %
Myopia > −5 00	9 3 %	15 9 %	0 8 %

Table III
Cataract operations Group A

Operation	Number of eyes
Intracapsular extraction	
a without α chymotrypsin	52 } ([illegible]9.2 %)
b with α chymotrypsin	9
Extracapsular extraction	
a. without needling	[illegible]
b with needling	2
Needling of congenital cataract	4
Unknown method	3
Total	(100 0 %)

not demonstrate the presence of more myopes than the PRD group from the same population possibly less (Table II) The precentage of high myopes is much higher however compared to a population of healthy young men in Sweden (Strömberg 1936)

The role of the operative technique and complications during and after the operation have also to be considered The intracapsular method was thought to be more dangerous (mechanical trauma during lens extraction by pulling the posterior attachments of the zonules vitreous detachment and displacement) Nonnenmacher (19.1) however did not find any evidence to show that the intracapsular extraction involves more risks than the extracapsular method The incidence of RD was in fact higher in a group of extracapsular extractions especially in high myopia The use of α chymotrypsin seems to increase the risk especially in myopic eyes (Berar cit by Tresster 19.2)

In the present study the presumed increased risk of the intracapsular method is not supported In the prospective study as many as three of the nine cases with ARD were operated on by the extracapsular technique in spite of only 16 % in the total series In the retrospective study the relative number of intracapsular extractions did not exceed the 84 % in the prospective study which is probably representative for the whole material (Table III)

Vitreous loss or vitreous haemorrhage at the time of operation are thought to increase the risk for fixed folds or massive vitreous retraction (Schepens 19.? Tolentino et al 196) In the prospective study four of the nine eyes with ARD and in the retrospective study 12 % were reported to have had vitreous loss

The interval between the cataract operation and the onset of RD is usually short which speaks in favour of the operation being an important cause of the RD In case of very early detection of RD it is sometimes impossible to know whether the RD was present before the cataract operation

Bagley (1948) found that 44 8 % of ARD occurred during the first six months Ashrafzadeh et al (19.3) found that 32 2 % developed within six months and 45 8 % within one year In our series six of the nine cases of RD in the prospective study had an interval of less than four months In the retrospective study *the intervals are shown in Fig 1 In 39 % the RD occurred* during the first six months and in .1 % during the first year

The prognosis of ARD is generally poorer than in PRD (Schepens 19.1 Witmer 1969) If cases with massive vitreous retraction are excluded the percentage of reattachment is nearly the same as in the PRD group (Schepens 1951) Norton s (1964) series of 424 consecutive cases of RD showed 85 % reattachments in the ARD group and 89 % in the PRD group i e a very small difference

Encircling procedures are generally thought to be more advantageous in

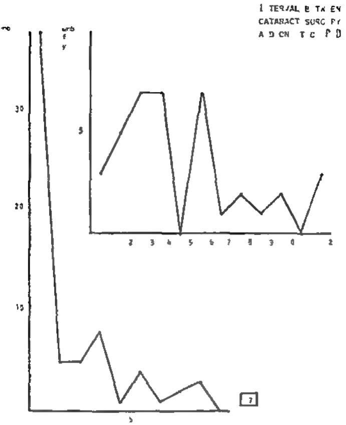

Fig 1

Interval between cataract operation and onset of retinal detachment in the retrospective study of 77 eyes with aphakic retinal detachment Lower curve Distribution of eyes during the first ten postoperative years Upper curve Distribution of eyes during the first postoperative year

Table II

Treatment Number of eyes

Group A only eyes with retinal detachment

Operation	Aphakic eyes	Phakic eyes
None	5	3?
Cerclage	48 (64 9 %)	15_ (29 6 %)
Other	?3	3?9
Total	74 (100 0 %)	513 (100 0 %)

Table I
Results of treatment. Number of eyes.
Group A: only eyes with retinal detachment

Results	Aphakic eyes	Phakic eyes	Significance $p < 0.05$
Reattachment	49 (66.2 %)	390 ([illegible]0 %)	No
Not cured	21	90	
Unknown	1	1	
No operation	3	3[illegible]	
Total	[illegible]4 (100 %)	513 (100 %)	
Reattachment in operated eyes	([illegible]0 %)	([illegible]1 %)	Yes

Table II
Postoperative visual acuity. Number of eyes.
Group A: only eyes with RD 19[illegible]1–[illegible]5*

Visual acuity	Aphakic eyes	Phakic eyes	Significance $p < 0.05$
1.0–0.[illegible]	11	48	
0.5–0.2	5	66	
0.1–3/60	6	36	
2/60–HM	[illegible]	23	
Light perception or less	6	12	
No operation	1	5	
Total	36	190	
≥ 0.2	45.7 %	61.6 %	No
$\leq 2/60$	3[illegible].1 %	18.9 %	Yes

* Follow up with visual function after six months available only in records from patients operated on during the last five years.

Table VII

Detachment area at the first examination Number of eyes Group A

Area	Aphakic eyes		Phakic eyes		Significance $p < 0.05$
No RD	3		207		
$\leq 90°$		4 (5.4 %)		91 (17.7 %)	Yes
$90°$–$270°$		46 (62.2 %)		340 (66.3 %)	No
$270°$–$360°$		24 (32.4 %)		82 (16.0 %)	Yes
Total	3	74 (100.0 %)	207	513 (100.0 %)	

ARD than in PRD In the present series such methods were used in about 2/3 of the eyes with ARD compared to 1/3 of the eyes with PRD (Table IV)

A significant difference (χ^2 method) between the percentage of reattachment in the operated eyes with ARD and PRD was found (Table V) Also the final visual acuity was less in ARD than PRD (the difference for severe loss of vision is significant) (Table VI)

A moderate difference in the prognosis of ARD and PRD is therefore probable Some characteristics of ARD may be responsible In many eyes retinal holes are not found sometimes because remnants of lens material prevent an exact ophthalmoscopy Vitreous strands after a complicated cataract extraction may produce retinal folds or other signs of traction A more liquid and mobile vitreous is probably the cause of the rapid increase of the detached area (Table VII) and may also prevent the reattachment

Conclusions

1 The incidence of retinal detachment after cataract surgery is 1.5–1.8 %

2 Intracapsular technique is probably not more dangerous than the extracapsular maybe less so

3 The interval between the cataract operation and the onset of retinal detachment is less than one year in 51 % many cases develop during the first 6 months

4 The percentage of myopic eyes is less in ARD than in PRD The difference is not significant however

5 The detached area is larger in ARD than in PRD at the first examination

6 The percentage of reattachment in operated eyes of ARD (69 0 %) is less than PRD (81 1 %)

The final visual acuity is less in ARD than in PRD

References

Ashrafzadeh M T Schepens C L Elzeneiny I I Moura R, Morse P H Kraushar M F (19 3) Aphakic and Phakic Retinal Detachment I M A *Arch Ophth 89* 4 6-483

Bagley C H (1948) *Retinal Detachment Amer J Ophthal 31* 285-298

B hringer H K (19 6) Statistisches zu Haufigkeit und Risiko der Netzhautablosung *Ophthalmol ica 131* 331-334

Nonnenmacher H (19 1) Über Netzhautablösungen nach Staroperationen *Klin Mbl Augenheilk 118* 5 3 5

Norton E W D (19 4) Retinal Detachment in Aphakia *Amer J Ophthal 58* 111-124

Okun E (1961) Gross and microscopic pathology in autopsy eyes *Amer J Ophthal 51* 3 391

Kulen M & Rajpurohit P (19) Distribution of myopia in aphakic retinal detachments *Brit J Ophthal 60* 51 571

Schepens C L (1951) Retinal Detachment and Aphakia I M A *Arch Ophth 45* 1 16

Stromberg E (1936) Über Refraktion und Achsenlange des menschlichen Auges *Acta ophthal (Kbh) 14* 281 291

Tolentino F I Schepens C L & Freeman H M (196) *Massive Preretinal Retraction I M A Arch Ophth* 16

Treister G (19 2) Prevention of Retinal Detachment in High Myopic Aphakic Eyes *Israel J Med Sci* 8 1434 1438

Tornquist R (1963) Bilateral Retinal Detachment *Acta ophthal (Kbh) 41* 126-133

Witmer R (19) Aphakie Amotio *Klin Mbl Augenheilk 1* 66 6

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VISUAL COMPLAINTS AND BINOCULAR FUNCTION IN BILATERALLY APHAKIC PERSONS WITH CATARACT GLASSES

BY

*ANDERS HVIDBERG and MARY ANN JENSEN**

Seventy one consecutive patients who underwent operation for senile cataract in both eyes during the period 1969–1973 were examined and questioned about visual complaints an average of 18 months after being fitted with cataract spectacles In the distance situation none had complaints either reported spontaneously or after questioning Except for a few immobile patients all could manage on their own in the street and on stairs

In the near situation 16 of the 71 patients had permanent alternating or intermittent exotropia which however gave rise to diplopic complaints in only two The *diplopia* in these two patients disappeared after the glasses had been decentered On questioning complaints of diplopia could be elicited in another 5 patients

Investigation of sensory binocular function using Titmus stereotest showed that 35 of the 71 patients could manage the test at the level 40 /arc

Division of the material into two groups by duration of monocular visual function during the development of the cataract and during the period between the operations on the two eyes disclosed that this factor was of no importance to the postoperative motor and sensory binocular function

Key words binocular aphakia – visual complaints – binocular vision – stereoacuity – diplopia

* Orthoptist

The purpose of the present study is to record any possible visual complaints in the binocularly aphakic patient with glass correction and to evaluate binocular function in such patients as well as the relationship between these factors. To our knowledge only one author has treated this subject before (Foster & Jackson 1933); the study included only ten patients.

Material

The material comprises 71 consecutive patients who underwent operation for senile cataract in both eyes during the period 1969–1973 and whose postoperative vision with optimal glass correction was 6/12 or better in the poorer eye. The patients' mean age was [illegible]4 years (range [illegible]6–90). Thirteen were males and 58 females.

Methods

The patients were examined from 5–30 months (on average 18 months) after having been supplied with cataract glasses for both eyes. If at follow-up the glasses were not of the correct strength or not correctly centered, the examination was repeated six weeks after the patient had been fitted with the optimal spectacles.

All the patients were questioned about visual complaints, if any, for distance and near. The questions were classified into two groups:

(1) Complaints of insecurity and of uncharacteristic dizziness, in some cases with a tendency to fall, i.e. complaints due to the restricted visual field, the annular scotoma and the altered assessment of distance as well as the distortion caused by cataract glasses.

(2) Periodical or permanent diplopia or shift in the localization of subjects seen, i.e. complaints due to defective binocular function.

The follow-up examination comprised the following elements:

(1) Determination of visual acuity for distance and near.

(2) Examination for phoria for distance and near (alternating cover test and prism bar).

(3) Examination for tropias for distance and near (monolateral cover test and prism bar).

(4) Examination of convergence function (with optimal reading glasses).

(5) Determination of fusion amplitude in the synoptophore.

(6) Determination of stereopsis using the Titmus stereotest.

Results

Complaints in the distance situation

At follow up from 5–30 months mean 18 months after operation for cataract in the second eye and subsequent fitting with cataract spectacles no patient had spontaneous visual complaints in the distance situation Even on questioning it was not possible to elicit complaints about visual function for distance Thus except for a few immobile patients all could move about on their own in the street and on stairs and none had any problems in watching television or in the cinema

Complaints in the near situation

After correction of intermittent exotropia for near in two patients by decentering the cataract glasses no patient had spontaneous complaints about the visual function for near In other words there were no spontaneous reading complaints in any patient in the entire series However when questioned about visual complaints for near 5 patients reported periodical diplopia while reading but this diplopia was of such a mild nature that none of the patients wanted treatment of any kind

The results of the examination for binocular function are given in Tables I and II and may be summed up as follows

One patient had permanent altering exotropia for distance but had no visual complaints i e he did not notice diplopia or localization shift

No patient had complaints due to the varying phorias in the distance situation

In the near situation 16 out of the 71 patients had permanent alternating or

Table I
Binocular function in the distance situation

	Number	Visual complaints
Exotropia permanent altern	1	none
Exotropia intermittent	0	
Exophoria > 8 pd	4	none
Phoria < 8 pd	66	none

Table II
Binocular function in the near situation

Motor status	Number	Stereoacuities (Titmus stereotest)		Visual complaints	
		6 " or worse	40" or better	binocular	others
Exotropia permanent	5	not tested		none	none
Exotropia intermittent	11	-	4	3 diplopia 4 diplopia	none
Exophoria > 5 pd poor fusion	6	6		none	none
Exophoria < 5 pd poor fusion	[illegible]	2		none	none
Exophoria > 5 pd good fusion	23	9	14	none	none
Exophoria < 5 pd good fusion	24		1	none	none
Esodeviation	0	0	0	0	0
Total	1	31	35		0

Good fusion is defined as a fusional range more than twice the heterophoria measured and also > 10

* Visual complaints i.e. reported either spontaneously or after questioning

intermittent exotropia. However, as already mentioned, this caused spontaneous complaints of diplopia in only two patients, and on questioning, complaints of diplopia could be elicited in only another 5 of these 22 patients. (About half of the patients spent many hours a day reading without any complaints.)

Investigation of stereopsis in the 66 patients who did not have permanent exotropia revealed that the Titmus stereotest could be accomplished at the level 40 /arc by 35 patients, i.e. half of the entire series had bimacular fusion.

* According to Parks (1966) this may be taken to indicate that these patients possess the ability for bimacular fusion.

Presumably the number of patients with bimacular fusion is larger than these 35 since owing to their advanced age and to the correspondingly somewhat reduced ability to cooperate the patients were perhaps unable to state the maximum stereovision

Division of the material into two groups according to the duration of mono cular visual function during the development of the cataract and during the period between the operations on the two eyes disclosed that this factor was of no importance to the postoperative motor or sensory binocular function

Discussion

The present study indicates that the discomfort of wearing cataract spectacles is considerably less than stated *int al* by the advocates of implanting intraocular lenses

At follow up an average of 18 months after being fitted with cataract spectacles for both eyes only two patients had spontaneous visual complaints viz diplopia in the near situation These complaints were obviated by de centering the glasses

Interviews with the patients more than six months after the operation on the second eye revealed that all considered the complaints were negligible after 2–6 months of getting used to the strong cataract glasses and that of the 71 bilaterally aphakic patients none felt visually disabled The defects in binocular vision did not cause any visual complaints It may thus be concluded that in the present material the usual discomfort of wearing cataract glasses disappeared spontaneously within the first months

References

Foster J & Jackson A S (1933) Aphakic stereoscopic vision *Brit J Ophthal 17* 93
Parks M M (1965) *Stereoacuity as an Indicator of Bifixation* Strabismus Symp Giessen pp 258–260 Karger Basel/New York

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Table II

Binocular function in the near situation

Motor status	Number	Stereoacuities (Titmus stereotest)		Visual complaints **	
		60″ or worse	40″ or better	binocular	others
Exotropia permanent	[illegible]	not tested		none	none
Exotropia intermittent	11	7	4	3 diplopia 4 diplopia	none
Exophoria > 5 pd poor fusion	[illegible]	6		none	none
Exophoria < 5 pd poor fusion	[illegible]	2		none	none
Exophoria > 5 pd good fusion	[illegible]3	9	14	none	none
Exophoria < 5 pd good fusion	21	[illegible]	17	none	none
Esodeviation	0	0	0	0	0
Total	[illegible]1	31	35		0

* Good fusion is defined as a fusional range more than twice the heterophoria measured and also > 16

** Visual complaints are reported either spontaneously or after questioning

intermittent exotropia. However, as already mentioned, this caused spontaneous complaints of diplopia in only two patients, and on questioning complaints of diplopia could be elicited in only another 5 of these 22 patients. (About half of the patients spent many hours a day reading without any complaints).

Investigation of stereopsis in the 66 patients who did not have permanent exotropia revealed that the Titmus stereotest could be accomplished at the level 40″/arc by 35 patients, i.e. half of the entire series had bimacular fusion*.

* According to Parks (1966) this may be taken to indicate that these patients possess the ability for bimacular fusion.

long term treatment with contact lenses in this age group (Daniels 19 4 Flick 1975)

There seems to be a critical age for prescribing contact lenses with benefit to unilateral aphakic children which varies from five to ten years (Lyle 1953 Ridley 1953 Frey et al 1973 Fagling 1976)

Thus in many cases attention has been focussed on the treatment of amblyopia Even in adult patients it seems to be difficult to obtain binocular function in all cases of unilateral aphakia The level of binocular function thus depends on how soon a contact lens can be supplied (May & Wolliscraft 1968 Flick 1975) although orthoptical treatment can lead to improvements (Vannas et al 1972) An examination of the binocular function at the time of lens fitting is important for the assessment of the benefit derived from contact lenses (Dreyer 1973) However an essential factor remains namely the attitude of both the patient and the parents (Daniels 1974)

Material

The aim of this study was to elucidate the prognosis for visual acuity and binocular function in children with unilateral traumatic aphakia All children under the age of ten years who were fitted with contact lenses because of unilateral traumatic aphakia at Ullevål Sykehus and Hamar Sjukehus were followed up They were reviewed by an ophthalmologist and an orthoptist on average three years after contact lens fitting

The material consists of seventeen patients (11 boys and 6 girls) When supplying these children with contact lenses emphasis had been laid on a clear pupil and a normal fundus At the time of lens fitting none of the patients were deeply amblyopic The binocular function with trial lenses was estimated by Worth 4 dot test In most of the cases either fusion or diplopia was found but some of the patients with suppression were also fitted with a lens A hard lens was initially tried when the corneal cicatrix permitted it When this failed a soft lens was resorted to In cases of amblyopia the children underwent periods of occlusion therapy

Methods

All of these seventeen patients attended follow up examinations Visual acuity with the contact lens was tested The eye position was estimated by prism cover test at 30 cm and 6 m Binocular function was estimated by Worth 4 dot test Bagolini lenses and Titmus stereotest Finally the patients were examined on the synoptophore

Table 1

Total results in follow up examination of 8 children wearing contact lens because of unilateral traumatic aphakia

Patient No	Age at injury in years	Months between injury and contact lens	Bifocal glasses	Prism correction	Squint surgery	Visual acuity	Covertest 6 m	Worth four dot 30 cm	Titmus stereotest	Binocularity in synoptophore	Orthoptical training	Follow up time (years)	Contact lens still in use
1	6	2		+	–	6/6	Exophoria	4	+1½	III	+	1½	++
2	7	12		+	–	6/9.5	Exotropia	4	–	II	–	1	++
3	8	3	+	–	–	6/9+	Exophoria	4	–	III	–	8	+
4	10	27	–	–	–	6/12+	Exotropia	Suppression	–	I	–	6	–
5	5	5	–	–		6/15	Exotropia Hypertropia	Suppression	–	I	–	8	+/–
6	4	24	–	–	–	6/12+	Exotropia Hypertropia	4	–	I	–	2	+
7	7	4	–	–	–	6/6+	Exophoria	4	++60	III	–	2	++
8	6	6	–	–	–	6/18	Exotropia	Suppression	–	I	–	[illegible]	–

9	8	24	+	+	–	6/10	Esotropia	4	–	II	+	1	+
10	8	3	+	+	+	6/8 .,+	Ortophoria	4	++ 80	III	+	3	++
11	5	[illegible]	–	–	–	6/12–	Exotropia	Suppression	–	I+	–	4	–
12	8	2	–	–	–	6/12	Exotropia	Suppression	–	I	–	6	–
13	6	5	+	+	–	6/12	Esotropia	4	–	III	–	3	++
14	8	6	+	–	+	6/12+	Esotropia Hypotropia	Diplopia	–	I	–	?	++
15	5	6	+	–	–	6/12–	Esotropia Hypertropia	Diplopia	–	I+	–	4	++
16	7	3	+	–	–	6/15	Exotropia	4	–	I+	–	2	+
17	7	1	+	–	–	6/9	Esophoria	4	++ 200	III	–	0 1	++

Patients No 1–12 are from Ullevål Sykehus
Patients No 13–17 are from Hamar Sjukehus
I Simultaneous perception II Fusion III Stereopsis

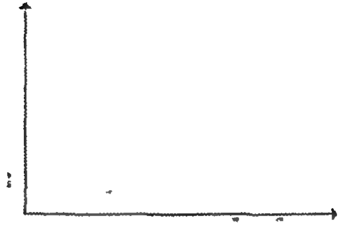

Fig. 1
Age distribution in [illegible] unilateral traumatic aphakic children fitted with contact lens

Results

All the results are shown in Table I. Age distribution is shown in Fig. 1. Table II shows visual acuity measured with contact lens.

None of the patients were deeply amblyopic. In some cases the corneal cicatrix may have affected the visual acuity measurement.

Eye position by Covertest at 6 m is shown in Table III.

Only one patient had orthophoria. The others mostly had phorias and tropias of less than 5 degrees. In four cases the horizontal squint was combined with a vertical deviation. Two patients had undergone squint surgery, five had prism glasses in front of their contact lenses. Ten patient had bifocal glasses while the contact lenses of the others had been overcorrected by approximately 1 diopter.

Table II
Visual acuity measured at follow up examination of 17 unilateral traumatic aphakic children treated with contact lens

< 6/18	6/18–6/12	6/10–6/6
0	8	9

Table III

Covertest at 6 m in 17 unilateral traumatic aphakic children treated with contact lens

Covertest 6 m	Number of patients
Exophoria	[illegible]
Esophoria	2
Exotropia	[illegible]
Esotropia	5
Orthophoria	1

Fig 2 shows the age of the patients at the time of injury in relation to later binocularity None of the patients who were under six years at the time of the injury showed stereopsis in the follow up examination on the synoptophore In the examination with Titmus stereotest only four of the seventeen showed stereopsis The degree of binocular function achieved in relation to the period between the injury and lens fitting is shown in Fig 3

None of the patients fitted later than six months after the trauma achieved stereopsis

Fig 4 shows the number of patients still wearing lenses in relation to the binocularity obtained

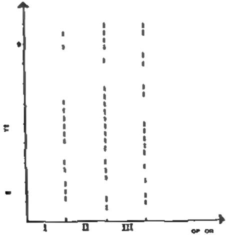

Fig 2

Binocular function in relation to age at the time of trauma in 17 unilateral traumatic aphakic children treated with contact lens I Simultaneous perception II Fusion III Stereopsis

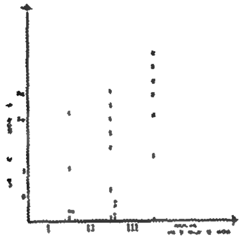

Fig 3

Binocular function in relation to the period from injury to the fitting of contact lens in 1 unilateral traumatic aphakic children I Simultaneous perception II Fusion. III Stereopsis CL Contact lens

All the patients were motivated for a continued use of contact lenses Four of them had given up using the lens after consulting their ophthalmologists at a time when occlusion therapy was completed and there was little change of binocular function being achieved

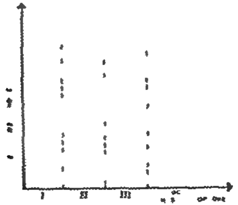

Fig 4

Binocular function in relation to continued wearing of lens in 1 unilateral traumatic aphakic children I Simultaneous perception II Fusion III Stereopsis CL Contact lens

Discussion

The results shown in this study are influenced by the fact that until recently access to an orthoptist has been difficult only three of the patients have received orthoptical treatment

Our conclusion is that the chance of obtaining good binocular function in unilateral traumatic aphakic children is greater the shorter the interval between injury and lens fitting In no circumstances should this period be longer than six months Active surgery to obtain a clear pupil as soon as possible is re commended

The contact lens initially a soft lens should be fitted as soon as possible In cases of amblyopia periods of occlusion therapy are necessary Squint may occur and is treated by surgery and prism glasses In some cases orthoptic treatment may be resorted to If binocular function is not obtained the contact lens can be discontinued when the risk of amblyopia is over

The future will show whether intraocular implant lenses will give a better prognosis for such patients The indication for intraocular implant lenses has been discussed for some years (Girard et al 1962 Binkhorst & Gobin 196[illegible] Nolan & Hawkswell 19[illegible]4 Eagling 1976) but the long term behaviour of these implants has yet to be evaluated

References

Binkhorst & Gobin (1967) Pseudophakia after Lens Injury in children. *Ophthalmologica 154* 81–87

Brændstrup (1944) Amblyopia exanopsia in infantile cataract *Acta ophthal (Kbh) 2[illegible]* 5[illegible]–71

Daniel (1974) An Evaluation of Contact lenses in unilateral post traumatic aphakic children *The Contact lens 4* 16–24

Dreyer (1973) The Binocular Vision as an indicator for the success of and need for unilateral contact lenses *Acta ophthal (Kbh) [illegible]1* 73[illegible]–739

Eagling (19[illegible]6) Perforating injuries of the eye *Brit J Ophthal 60* [illegible]32–[illegible]36

Flick (19[illegible]5) Die einseitige Aphakie im Kindes Alter *Klin Mbl Augenheilk 167* 664–669

Frey et al (1973) Re evaluation of monocular cataracts in children. *Amer J Ophthal [illegible]6* 381–388

Girard (1962) Intraocular implants and Contact lenses *Arch Ophthal (Chicago) 68* 762–775

Lyle (19[illegible]3) The Importance of orthoptic Investigation before Contact lens fitting in unilateral aphakia *Trans ophthal Soc U K 73* 38[illegible]–398

May & Wolliscraft (1968) Corneal contact lenses in traumatic unilateral aphakia. *Canad J Ophthal 3* 231–[illegible]36

McKinna [illegible] Results of Treatment of traumatic cataract in children. *Amer. J. Ophthal.* [illegible]

Nolan [illegible] Hawkswell (19[illegible]) Clinical aspects of unilateral aphakia. *Trans. ophthal. Soc. U. K.* [illegible]

Ridley (19[illegible]) Contact lenses in unilateral aphakia. *Trans. ophthal. Soc. U. K.* [illegible]

Yannas et al. [illegible] Binocular vision in monocular aphakia correctible by contact lenses. *Acta ophthal. (Kbh.)* [illegible]

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The Department of Ophthalmology
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UNILATERAL TRAUMATIC CATARACT IN CHILDREN

BY

ANNE K SJOLIE and K KAMP MORTENSEN

A survey is presented of the course of unilateral traumatic cataract in 15 children of 8 years of age and below admitted consecutively to the Ophthalmological Department of the Odense University Hospital over a period of 9 years The follow up examination revealed that four patients had visual acuity of more than 6/18 and of these two retained binocular single vision and used contact lenses
The size of the material does not permit any conclusive statements to be made Thus it is impossible to select the patients who will have either a good or a poor final result from the treatment with regard to vision and binocular single vision

Key words traumatic cataract – children – amblyopia – contact lenses – deviation – binocular single vision

The prognosis of unilateral traumatic cataract in children has only rarely been mentioned in the literature Juler (1921) found among 14 children below the age of [illegible] years one patient with visual acuity of 6/9 and four patients with a visual acuity of less than 6/12 as best results McKinna (1961) was able to demonstrate in a study of 26 patients below the age of 7 years that only one had visual acuity of 6/9 Frey et al (1973) reported on 17 patients under the age of 9 years of these five patients had visual acuity of 6/9 or better of which four used contact lenses Greenstein (1976) found in 12 patients below the age of 9 years who were considered suitable for the fitting of contact lenses five patients with a good prognosis with regard to visual acuity

Material and Methods

The present material comprises all the patients admitted to the Ophthalmological Department of the Odense University Hospital during the period 1.4.67 to 31.3.76. *There are 15 children between the ages of 3 and 8 years at* the time of the accident.

In eight patients the trauma was caused by a sharp metal object, in five by a wooden object and in two cases the cause was unknown.

On admission 14 patients were found to have a corneal perforation and one a contusion of the eye. Of these, 12 had an affected lens at the time of examination, while in three others the cataract did not appear until later. Only one of the children had an intrabulbar foreign body.

The average duration of hospitalization was 28 days, the average number of outpatient control examinations 19 (range 5 to 36), and the average period of observation 16½ months (range 1½ to 54 months).

Three patients had to be excluded from the material owing to enucleation, one because of total detachment of the retina and one patient did not wish, for psychological reasons, to participate in the follow up examination.

Ten of the patients were treated with hard contact lenses and/or occlusion as soon as possible, as shown in Table 1, in order to avoid the development of amblyopia. One was referred to his own ophthalmologist for further treatment; he did not consider it necessary to give prophylactic treatment for amblyopia.

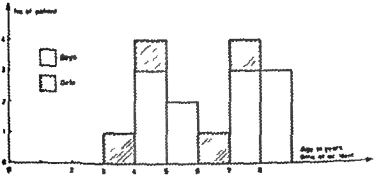

Fig. 1
Age and sex distribution.

Table I

Pat No	Age	Exam on admission	Primary treatment	No of ops	Time in months	Amblyopia prophylaxis
1	3	corneal perf + cataract	wound suture	[illegible]	4 1/2	occl
2	4	contusion of eye	no operation	1	5 /2	occl CL
3	5	corneal wound CWE + cataract	no operation	1	9 1/	occl CL
4	5	corneal perf + cataract	wound suture	1	1 1/	occl
5	[illegible]	corneal perf + cataract	wound suture	2	14 /2	occl CL
6	7	corneal perf + cataract	wound suture	1	5	occl
7	7	corneal wound CWE + cataract	no operation	3	10	CL
8	7	corneal perf	wound suture	2	16	CL
9	7	corneal wound CWE + cataract	no operation	2	4 1/	CL
10	8	corneal perf + cataract	wound suture + aspiration	3	4 1/	non
11	8	corneal wound CWE + cataract	no operation	3	6	CL
12	4	corneal wound CWE	no operation	1	1 1/	none
13	4	corneal perf + cataract	no operation	1	1 1/	none
14	4	corneal perf + D L	wound suture	1	2 1/	none
15	5	corneal perf + cataract	wound suture	1	[illegible]	none

Time = time interval from accident until clear ocular media CWE = clean wound edges
Occl = occlusion D L = dislocated lens CL = contact lenses Ops = operations

Ten patients were re called for follow up examination in August 19/6 Examination of the ocular media was carried out in all patients as well as an examination of the retina The orthoptic examination included the star test cover test at 30 cm and 6 m prism cover measurements the Worth 4 dot test and evaluation of fusion and stereopsis by means of the synoptophore and Wirt fly test

Table II
Results of follow up examination

Pat. No.	Visual acuity	Media	Back-ground	Phoria/tropia of damaged eye	Fixation	BSV
1	1/12	clear	normal	10° exotropia	searching	none
2	>6/18 CL	clear	normal	< 5° exophoria	central	+
3	3/24	clear	normal	15° exotropia ⊃ 2° hypertropia	central	none
4	>3/24	clear	normal	exotropia ⊃ slight hypertropia	searching	none
5	F.C.	A.C.	V.O.	25° exotropia	eccentric	none
6	6/24	clear	normal	12° exotropia ⊃ slight hypertropia	searching	none
	>6/24	clear	normal	6° exotropia ⊃ 4° hypertropia	searching	none
8	>6/6 CL	clear	normal	none	central	+
9	2/36	clear	V.O.	30° exotropia ⊃ 2° hypertropia	searching	none
10	6/9	clear	normal	10° exotropia ⊃ slight hypertropia	central	none

BSV = binocular single vision = stereoptic perception of the big fly. CL = contact lenses.
F.C. = finger count. A.C. = after cataract. V.O. = vitreous opacity.
The visual acuity stated is that measured with optimal correction and without the use of a stenopaeic hole.

Results

As can be seen from Table II, four patients had a visual acuity of more than 6/18; the others had poorer vision.

Two patients used contact lenses constantly, with a visual acuity of 6/6 and more than 6/18, and both were satisfied with the lenses. There is one further patient who is at present undecided as to whether or not contact lenses can be used permanently.

It can in addition be seen from Table II that the optical conditions following surgery were good inasmuch as there were clear ocular media in all those followed up apart from one patient who had a secondary membrane in the pupil.

In two patients corpus vitreum membranes were present which impaired central vision One of these two was the patient with a secondary membrane in the pupil Normal eye backgrounds were found in the other patients

Exotropia of varying degrees was found in eight of the patients in six of these combined with slight hypertropia

Four of the patients had central fixation three of whom had good vision One patient had eccentric fixation and searching fixation was observed in five

Such binocular function as fusion and stereopsis with the Wirt fly test was observed in two patients namely those two with contact lenses and good visual acuity

We have chosen to define the limits of amblyopia as 6/18 It can be seen from Table II that seven of the patients had vision of less than 6/18 but of these two had organic changes that could explain the poor vision Thus amblyopia developed in five patients

We have divided our material into two groups and compared the final visual acuity in patients of less than 6 years and those of 6 years and above No significant difference in the prognosis with regard to the development of amblyopia could be demonstrated between these two groups by means of the Fisher s exact test

Discussion

In cases of traumatic cataract in children the ideal objective is to produce optimal optic conditions as rapidly as possible in order to retain binocular single vision

Frey et al (1973) state that the treatment of choice is prompt aspiration followed by the fitting of contact lenses

Greenstein et al (1976) conclude that the significant factor in the development of amblyopia which prevents the restoration of binocular single vision is the age at which trauma occurs The same authors find no relationship between visual acuity and the time lapse from trauma to contact lens fitting

With our small material it has not been possible to demonstrate any relationship between the age of the patient at the time of the accident and the development of amblyopia Neither have we been able to find any correlation between the vision and the time interval between the accident and the obtainment of good optical conditions

It can be seen from Table II that two of our patients had retained binocular single vision and in addition that two patients had visual acuity above the limit set for amblyopia Five patients had developed amblyopia three had

been treated with occlusion of the latter one had temporarily used contact lenses. As amblyopia was not primarily present in the other two they were only fitted with contact lenses. The use of these contact lenses was however discontinued later owing to continued local irritation and also because of diplopia.

As can be seen from Table II all the patients except one who had parallel positioning of the eyes had exodeviation. This is in contrast to other authors who find a more or less equal distribution between eso- and exodeviation.

Conclusion

An evaluation of the results in relation to the amount of effort required – particularly from the child and parents – would suggest that it is a difficult and time consuming treatment which can produce considerable psychological problems for the child, furthermore it is far from certain that good results can be obtained. However we consider that an attempt should be made to motivate the patient and parents to co-operate in the treatment inasmuch as it is impossible to predict the final result with regard to visual acuity and binocular single vision.

Acknowledgments

We thank orthoptician Miss Jytte Kirkegård Nielsen for participating in the orthoptic analyses.

References

Frey T, Friendly D & Wyatt D (19[illegible]3) Re-evaluation of monocular cataracts in children. *Amer J Ophthal* 7[illegible] 3[illegible]1–3[illegible]
Greenstein S, Goldstein J H, Adler K I & Karp F (19[illegible]) Prognosis for binocular vision in monocular trauma. *Brit orthopt J* 3[illegible] 44–[illegible]
Juler F (1921) Amblyopia from disuse. Visual acuity after traumatic cataract in children. *Trans ophthal Soc U K* 41 1[illegible]9–139
McKenna A J (196[illegible]) Results of treatment of traumatic cataract in children. *Amer J Ophthal* [illegible] 43–53

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SOCIAL AND MEDICAL ASPECTS OF UNILATERAL TRAUMATIC APHAKIA

BY

TOVE HAGHFELT and E GOLDSCHMIDT

Twenty one males between 16 and 50 years of age were admitted during a five year period and treated for a corneal perforation and traumatic cataract One did not attend the follow up examination Five patients were not offered contact lens owing either to their occupation or to bad visual acuity Twelve patients were offered contact lens but only four patients made permanent use of them and have good binocular function Three patients were given an intraocular lens two of these with good results
Many of the patients had considerable problems at work and there appears to be a certain amount of relationship between the length of the sick leave and their later employment Half of the patients had to change their occupation either totally or partly
Social security and social problems are discussed

Key words traumatic cataract – unilateral aphakia – contact lenses – binocular function – social aspects

It is well known that prolonged illness and subsequent inactivity makes a patient reluctant to resume work it is also well known that industrial accidents followed by disablement tend to make the patient disinclined to resume their former employment

We have considered with the above in mind that it would be of interest to carry out a study of a group of patients who have been the victims of an accident resulting in perforation of an eye with subsequent traumatic cataract In our opinion this should be carried out with regard to both the medical and the social aspects

Material

The basic material consists of all the patients admitted during a five year period (1.4.1965–1.4.1970) to the Ophthalmological Department of the Odense University Hospital with a perforating lesion of the eye and subsequent traumatic cataract. The follow up examination was carried out in the latter part of 1975.

There were 70 patients in all and Table I shows the age and sex distribution.

The main object of the investigation was from a medical and social aspect to study all the males between the ages of 16 and 50 years who in addition to the primary treatment were admitted and operated on for traumatic cataract in order to restore binocular vision. There were 40 males between the ages of 16 and 50 years among the 70 patients. Twenty one of the 40 were treated for traumatic cataract. The other 19 sustained such severe damage to the eye including vitreous haemorrhage and secondary reaction that it was obvious from the start that vision could not be restored.

One of the 21 patients treated for traumatic cataract did not attend the clinic for the follow up examination and therefore the present investigation consists of 20 patients.

Table II shows that 1[illegible] of the cases included in the study were industrial accidents. Thirteen of these patients had a ferro magnetic intrabulbar foreign body.

The majority of the patients were admitted to hospital within the first 24 hours of the accident. The foreign body was removed and primary suture carried out. Four patients were admitted considerably later as the primary trauma had been ignored; these patients were not seen by an ophthalmologist until a traumatic cataract had developed and reduced vision. Three of these patients had a foreign body in the eye when first examined.

Table I
Age and sex distribution

Age	Male	Female
< 16 years	15	4
16–50 years	40	3
> 50 years	8	0
Total	63	[illegible]

Table II
Perforating agent and time of accident

	No	At work	Spare time
Iron	15 (13)	14	1
Glass	2 (0)	0	2
Various (plastic wood etc)	3 (0)	3	0
Total	20 (13)	17	3

Ciffers in brackets indicate numbers of radiological positive intrabulbar foreign bodies

The cataract was not treated during the primary admission but the patients were re admitted for this operation at a later date The method of treatment of the cataract varied between discission linear extracapsular and in a single case intracapsular lens extraction Most of the patients were subjected to more than one operation The substance of the lens was spontaneously resorbed in one patient An intraocular lens was inserted according to the method of Bink horst in three cases Secondary glaucoma developed in one patient and required additional operations

The fellow eye was normal with normal vision in all the patients

Methods

The follow up examination included visual acuity measured with trial lens or contact lens reading vision slit lamp examination ophthalmoscopy and bino cular function the latter by means of the major amblyoscope and the Titmus tests Finally the amount of exophoria or exotropia was measured

The social invest gation was in the main carried out by E Thorning Lund a social worker and this provides information regarding the patient s employ ment economy and family

Results

Table III shows the visual acuity of the damaged eye at the time of the follow up examination the results being divided into three groups those with visual acuity better than 6/18 between 6/18 and 6/36 and less than 6/36 All

Table III
Visual acuity of injured eye

Corrected acuity	No
> 6/18	12
6/18–6/36	5
< 6/36	3

The visual acuity stated above was measured by trial lens, contact lens or intraocular lens.

the patients in the first and two of the patients in the second group had good reading vision. The causes of the reduction in visual acuity are shown in Table IV; some of these may be competitive.

It should be noted that owing to unilateral aphakia only a few patients were able to utilize their corrected visual acuity. All the patients with reasonably good vision were offered a contact lens. Unfortunately only four of the patients used a contact lens continuously at the time of the follow-up examination; the other 8 had stopped using it owing to diplopia, aniseikonia, conjunctivitis or dusty work (Table V).

All 20 patients had developed a secondary diverging strabismus or exophoria, varying between 2° and 20°; two of these patients had later been operated on for this condition. Only the four patients who continuously used contact lenses and two of the three patients with an intraocular lens had good binocular

Table IV
Cause of reduced vision

Cause	No. of pat.
Corneal astigmatism ≥ 2.0 cyl.	12
Secondary cataract	4
Vitreous haemorrhage	1
Scar in the fovea	1

Some of these are competitive causes.

Table V
Offer and use of contact lenses

	No
Not offered because of dusty work or bad vision	5
Offered and attempted could not use	8
Offered and continuous use	4
Intraocular lenses	3

function and stereopsis one 400 seconds and five better than 100 seconds The third patient with an intraocular lens suppressed the damaged eye

Two thirds of the patients complained of photophobia and several stated that *they would have preferred to be blind in the damaged eye rather than* being plagued daily by light and diplopia

There is no connection in this material between the length of sick leave and the later visual status

One patient with an intraocular lens (the one who suppressed the damaged eye) and one patient with a permanent contact lens have both changed their occupation and have made use of the rehabilitation services

The results of the investigation by the social worker showed that the majority of patients had difficulties on their return to their previous employment and that there appears to be some relationship between the length of the sick leave and the problems encountered on their return to work, see Table VI

Table VI
Social outcome in relation to sick leave

Duration (months)	Field of activity			Rehabilitation
	Unchanged	Partly changed	Changed occupation	
< 3 (N = 8)	5	3	0	0
3–6 (N = 6)	3	1	[illegible]	0
> 6 (N = 6)	[illegible]	1	3	3
Total (N = 20)	10	5	5	3

Only one patient had problems with the family as a result of the accident and the long period of sick leave. None of the other patients had any difficulties in this respect.

The eye injury had serious effects on the economy of many of the patients. Only three of them received their full salary during the period of sick leave, all the others had a reduced income during this period. This applied in particular to those patients who were self employed, as the social security programme at that time did not cover these persons.

The majority of the patients were covered by the compulsory employers liability insurance, the remainder were fortunate enough to have a private accident insurance. Thus all the patients received a reasonable amount of money in compensation for the damaged eye.

The social security act in Denmark has been ammended after completion of this study, so that now there is little economic risk for such patients, although the self employed man still has to pay for this coverage.

Discussion

The present investigation demonstrates that patients with corneal perforation and subsequent traumatic cataract obtained good visual acuity within a reasonable period after the accident, often within one year. Several operations were required in order to obtain these results.

The study also showed that, although the results of the treatment from the medical point of view were satisfactory in the great majority of cases, few of the patients had any real benefit from the medical treatment, which had involved long periods of hospitalization and considerable financial strain for the patients, in addition to difficulties on their return to work.

The reason for this is first and foremost that these patients have problems with binocular vision. Lyle (1954) concluded that an estimation of the binocular function by means of an orthoptic examination of the unilateral aphakic patient was of the greatest importance for the prognosis and success of the treatment. Dreyer (1973) carried out a study of 95 patients with unilateral aphakia (75 as a result of injury) who, wearing a trial contact lens, were examined in the major amblyoscope prior to the final prescription of a contact lens and came to the same conclusion.

According to Ridley (1953) the presence or absence of suppression is more dependent upon the time interval from injury to cataract operation than from operating to the fitting of the contact lens. This is in agreement with the

results obtained in a study carried out by Greenstein (1976) even though the latter was mostly concerned with the problems arising during childhood

All the patients in the present study were only offered contact lenses of the hard type and these are still considered the most suitable for aphakic patients even though soft hydrophilic lenses were available As mentioned by Greenstein (1976) soft lenses are most suitable for children and patients with marked corneal irregularities who are unable to tolerate the hard contact lenses

Little has been said in other investigations of the social consequences of this type of accident mainly owing to the fact that the social security laws differ from country to country However one of the main objects of the present investigation was to study the efficacy of the social security services in regard to patients who are the victims of this type of accident and to ascertain the effect of the accident on employment

Conclusion

The rather disappointing results of the attempts by the medical profession to restore good binocular vision in patients with traumatic cataract may raise the question whether or not the ophthalmologist is too active in his desire to obtain complete visual rehabilitation of the patient Also whether it would not be more reasonable to individualize the treatment and to focus more attention on rehabilitation of the patient with regard to future employment possibly with the help of industrial consultants and in suitable cases to abandon cataract extraction – and with this shorten the period of sick leave – in those cases where it is obvious from the start that the use of contact lenses is unfeasible owing to the patient s occupation unless of course there are other reasons for carrying out the operation for example glaucoma

The present material has shown even though it is rather small that unilateral aphakia often produces complications with regard to vision in addition to those occurring in respect of the patient s occupation Further that only approximately one third of the patients (six two with an intraocular lens) benefitted from the operation and the fitting of a contact lens Similar results have been obtained in other investigations of this type

References

Dreyer V (1973) The binocular function as an indicator for the success of and need for unilateral contact lenses *Acta ophthal (Kbh) 51* 73?–739

Greenstein V et al (1976) Prognosis for binocular vision in monocular trauma *Brit Orthopt J 33* 44–4?

Lyle T K (1953) The importance of orthoptic investigation before contact lens fitting in unilateral aphakia A preliminary report *Trans ophthal Soc U K* 73 387-398
Ridley F (1953) *Trans ophthal Soc U K* 73 515
Stone J (1972) Indications and contra indications for contact lens wear In Stone and Phillips *Contact lenses* 115-155 Barrie & Jenkins London

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CORRECTION OF APHAKIA WITH INTRAOCULAR LENS IMPLANTS

BY

ULF KRAUSE

40 cases of intraocular lens implants are reported. 33 % had an optimal post operative vision of >1.0, 56 % and ≥0.9 and 84 % 0.5 or better. After a postoperative follow up of 1 month to 32 months, mean 15.1 months, the patients were all satisfied with the pseudophakic eye, and no endothelial corneal dystrophy, chronic uveitis or glaucoma was detected. Several minor post operative complications were seen, most without consequence. One case had recurrent iridial haemorrhages.

Key words: intraocular lens implants – aphakia – visual results

Surgeons working with lens implants generally approve the statement: the primary complication of cataract surgery is aphakia. The result is inevitably a visually handicapped individual suffering from aniseikonia, ring scotoma, spherical aberration, lack of accommodation, problems related to binocularity, etc. All of these difficulties except the lack of accommodation may in principle be avoided by an intraocular lens implant. Functionally, the implanted lens is thus an ideal solution, but is the use of implants in other respects acceptable?

Subsequent to the implantation of the first posterior chamber intraocular acrylic lens by Ridley in 1949, the angle supported lens type was developed. This new method for the correction of aphakia was rapidly adopted by many well known surgeons. In 1958 the first reports on complications were given by Strampelli followed by many others, and within a few years the initial great enthusiasm for intraocular lens implants changed to violent opposition, since many very serious complications had been observed. It was later discovered that the fundamental reason for most of these was pressure induced endothelial

dystrophy caused by the angle supported fixation devices leading to progressive endothelial dystrophy, bullous keratopathy, iritis and secondary glaucoma, sometimes necessiting an enucleation.

Binkhorst then introduced in 1958 an entirely different type of fixation of the lens to the iris diaphragm, namely his iris clip lens, centred to the optic axis by the sphincter muscle (Binkhorst 1975). As a result the frequency of the most serious of the complications, the endothelial dystrophy, dropped dramatically and is now at the 0.6–2.56% level (Nordlohne 1974).

The problem of the toxicity of the implanted lens is a minor one: certain war casualties, tissue culture analyses (Cahn et al. 1975), postmortem histological studies (Manschot 1974, Jaffe 1976) and independent follow up studies (Pearce 1972) show that lenses of polymethylacrylate should be tolerated adequately and not cause an irritative iridocyclitis. Endothelial microscopy has not shown any progressive dystrophy of the endothelial cells (Forstot 1976).

It thus seems reasonable to accept the early discouraging results as being induced by pressure on the endothelial cells, in which case the application of iris supported or iridocapsular lenses is justified.

The fact that there are lens designs which are more suitable than others does not alter this argument.

Material and Methods

40 primary iris supported lens implantations were carried out at the Department of Ophthalmology, University of Oulu, between May 1974 and January 1st 1977 using the Medallion lens of Worst with fixation to the iris by a perlon suture. Thirty nine of these lenses had a refraction power of 20 and one of 23 diopters. The mean post operative observation time was 15.1 months (range 1–32 months). 30 cases were intracapsular extractions and 10 extracapsular extractions in young patients. Two patients had bilateral lens implants.

The main indication for lens implantation was unilateral cataract in connection with advanced age and expected difficulties in adaptation to glass correction, or even occupational demand for binocularity.

Results

The visual results are given in terms of the optimal post operative vision corrected with glasses. One case has not been seen post operatively.

Thirteen patients now have a vision of > 1.0 (33%) and 22 have ≥ 0.9

Table I
Optimal post operative vision corrected with glasses in 39 cases of intraocular lens implant

Post operative vision	Number of cases	%
> 1 0	13	33
0 9–1 0	9	23
0 7–0 8	6	16
0 5–0 6	5	13
0 3–0 4	4	10
0 1–0 2	–	–
< 0 1	2	5
Total	39	100

(56 %) 84 % (33 patients) have a vision of 0 5 or better (Table I) Two patients with a vision of < 0 1 have post traumatic vitreous opacities and a cloudy corneal graft respectively

Seven of the patients were emmetropic post operatively The mean post operative residual refraction (refractive error) was –0 4 D (range –5 0 to +3 75 D) All the patients have become accustomed to their intraocular lenses without any difficulty or binocularity problems A few have complained of some photophobia

The post operative complications that have emerged will be dealt with in three groups

1) those caused directly by the artificial lens
2) those not caused by the lens but aggravated by its presence
3) those independent of the lens

1) Dislocation of one loop of the lens into the front of the iris six patients two of them with slight traumatic mydriasis All the lenses were repositioned after mydriatics and pilocarpine though some also needed indentation of the cornea

One patient had recurrent hyphaema caused by an anterior synechiae the edge of the lens eroding some vessels of the iris Coagulation with a laser was not successful and the synechiae had to be released with a Ziegler knife

dystrophy caused by the angle supported fixation devices leading to progressive endothelial dystrophy, bullous keratopathy, iritis and secondary glaucoma, sometimes necessitating an enucleation.

Binkhorst then introduced in 1958 an entirely different type of fixation of the lens to the iris diaphragm, namely his iris clip lens, centred to the optic axis by the sphincter muscle (Binkhorst 1975). As a result, the frequency of the most serious of the complications, the endothelial dystrophy, dropped dramatically and is now at the 0.6–2.56% level (Nordlohne 1974).

The problem of the toxicity of the implanted lens is a minor one: certain war casualties, tissue culture analyses (Calm et al. 1975), postmortem histological studies (Manschot 1974, Jaffe 1976) and independent follow up studies (Pearce 1972) show that lenses of polymethylacrylate should be tolerated adequately and not cause an irritative iridocyclitis. Endothelial microscopy has not shown any progressive dystrophy of the endothelial cells (Forstot 1976).

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References

Binkhorst C (1975) Evaluation of intraocular lens fixation in pseudophakia *Amer J Ophthal 80* 184–191

Forstet S (1975) Corneal endothelial effects of lens implantation Audio Digest Foundation *Ophthalmology 14* No 24

Galin M Chowchuvech E & Galin A (1975) Tissue culture methods for testing the toxicity of ocular plastic materials *Amer J Ophthal 79* 665–669

Jaffe N S (1976) *Cataract surgery and its complications* p 133 2nd ed Mosby St Louis

Manschot W A (1974) Histopathology of eyes containing Binkhorst lenses *Amer J Ophthal 77* 856–871

Nordlohne M E (1974) Diss The intraocular implant lens Development and results with special reference to the Binkhorst lens *Docum ophthal 38* Issue 1

Pearce J L (1972) Long term results of the Binkhorst iris clip lens in senile cataract *Brit J Ophthal 56* 319–331

Ridley H (1951) Intraocular acrylic lenses *Trans ophthal Soc U K 71* 617–621

Strampelli B (1958) Cited by Nordlohne (1974)

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RESULTS FROM LENS IMPLANTATION

A material from four Danish hospitals

BY

LAUST H BAGGESEN ANNA MARIE LAND and
NIELS VESTI NIELSEN

*A retrospective evaluation of the results obtained with primary implanta*tion of an iris clip lens performed in four Danish eye departments [illegible] given Altogether [illegible]03 implants were carried out The mean age of the patients at the time of operation was [illegible] years Seventeen patients had bilateral implantation Besides the cataract the age of the patients was main indication for implantation Contributing indications were monolateral cataract macular degeneration and general somatic or psychic incapacity The incidence of more serious complications was (more than one complication [illegible] some eyes) corneal dystrophy 13/203 deposits on the clip lens or in the pupil 18/203 secondary glaucoma 2/203 macular oedema [illegible]/203 late recurrent hyphaema 2/203 and dislocation of the clip lens [illegible]/203 Seven clip lenses were removed A corrected visual acuity of 6/12 or above was found in 56 % of the cases postoperatively In spite of the complications it [illegible] considered justifiable to continue with clip lens implantation in elderly patients to solve the optical problems following aphakia

Key words cataract extraction – pseudophakos – iris clip lens – complications – visual acuity

Primary implantation of an iris clip lens – the theoretically ideal solution to the optical problems following aphakia – has until now only been used to a limited extent by Danish cataract surgeons It was therefore considered to be of interest to collect the experience with clip lenses from four Danish eye departments A report is given on indications and complications and the final results are evaluated

Material and Method

The material was collected from four Danish eye departments It consisted of eyes operated on for cataract with primary implantation of an iris clip lens traced from the operation lists The number of operations performed in the different departments appears from Table I Altogether 203 eyes were operated on Seventeen patients had bilateral implantations The ages of the patients ranged from 14 to 95 years with a mean age of 67 years at the time of operation Diagnoses were senile or presenile cataract 196 traumatic cataract 5 radiational cataract 1 and heterochromy cataract 1

The hospital records contained follow up examinations of short duration in all cases A further follow up examination comprising visual acuity slit lamp examination and ophthalmoscopy was made in 159 eyes The remaining 44 eyes were not examined as the patients did not come when requested Thirteen of the patients had died Range of observation time is from half a month to 72 months mean observation time 13¹/₂ months including all 203 eyes

Table I

Number of implantations performed in four Danish eye departments and date of first operation

	Number of operations	1 operation
Centralsygehuset Nykøbing F	2	27 2 6
Frederiksberg Hospital	93	25 1 73
Odense Sygehus	54	3 3 70
Rigshospitalet	24	7 2 73

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RESULTS FROM LENS IMPLANTATION

A material from four Danish hospitals

BY

LAUST H. BAGGESEN, ANNA MARIE LAND and NIELS VESTI NIELSEN

A retrospective evaluation of the results obtained with primary implantation of an iris clip lens performed in four Danish eye departments is given. Altogether 203 implants were carried out. The mean age of the patients at the time of operation was [illegible]7 years. Seventeen patients had bilateral implantation. Besides the cataract, the age of the patients was main indication for implantation. Contributing indications were monolateral cataract, macular degeneration and general somatic or psychic incapacity. The incidence of more serious complications was (more than one complication in some eyes): corneal dystrophy 13/203, deposits on the clip lens or in the pupil 19/203, secondary glaucoma 2/203, macular oedema [illegible]/203, late recurrent hyphaema 2/203 and dislocation of the clip lens 6/203. Seven clip lenses were removed. A corrected visual acuity of 6/12 or above was found in 56 % of the cases postoperatively. *In spite of the complications it is considered justifiable to continue with clip lens implantation in elderly patients,* to solve the optical problems following aphakia.

Key words: cataract extraction – pseudophakos – iris clip lens – complications – visual acuity

Table III
Postoperative complications in 43 eyes interfering with the end result

Corneal dystrophy	13
Opacities on the clip lens or in the pupil	18
Secondary glaucoma	2
Macular oedema	[illegible]
Late recurrent hyphaema	2
Dislocation of the clip lens	6

Corneal dystrophy was seen in 13 eyes In 10 eyes the dystrophy was due to contact with the implanted lens (shallowing of the anterior chamber occurred in 27 eyes) In three eyes where contact with the clip lens was not observed the dystrophy was presumably due to corneal damage (one following late ulceration of the cornea one in an eye with simple glaucoma with normal pressure on treatment and one after a luxated lens had been removed at another eye clinic) In the 13 eyes affected corneal dystrophy was slight in five eyes involving the upper part only but nevertheless reducing visual acuity In the remaining eight eyes the cornea was profusely involved

Opacities on the clip lens or in the pupil interfering with visual function occurred in 18 eyes of which eight showed deposits on the clip lens eight showed formation of a membrane in the pupil and two had remnants of corticalis in resorption The opacities either followed early hyphaema noted in 17 eyes or uveitic reaction (17 eyes) which was severe in two eyes with hypopyon and in three eyes with fibrin In three eyes recurrent episodes of slight uveitis were noted

Two patients developed secondary glaucoma with an intraocular pressure above 25 mmHg one of these ultimately had the eye enucleated due to pain A transistory rise in intraocular pressure was noted in 15 eyes In four eyes with simple glaucoma no rise in pressure was seen

Macular oedema was suspected in six eyes as visual acuity fell albeit only temporarily in four of the eyes The ophthalmoscopic examinations taken from the records showed nothing abnormal Macular oedema might however have occurred in some eyes which later showed central degeneration at follow up examination Retinal detachment was not seen

Late recurrent hyphaema occurred in both eyes of a patient with bilateral

clip lens implantation. On examination bleeding was seen from the irises where they had been eroded by the loops of the clip lenses.

In six cases dislocation of the pseudophakos was found. One was replaced with an iris hook. Two were left in the dislocated position with three loops in front of the iris as there was no reaction in the eyes. As previously mentioned one of these clip lenses was later removed at another eye clinic. Three luxated clip lenses were removed shortly after the implantation.

Reoperations were performed in 19 eyes, three of which were reoperated on twice and one several times (Table IV). Removal of the pseudophakos was performed in 7 eyes, four due to dislocation of the clip lens (delt with above) and three due to corneal dystrophy. As mentioned, *replacing* of a clip lens was done in one eye. Discission of a secondary cataract behind the clip lens was performed in three cases. Synechiolysis was done in three eyes with corneal dystrophy, the clip lens was later removed from one of these eyes. A peripheral iridectomy was performed once in three eyes and twice in one eye to reestablish the anterior chamber as the original iridectomies had been blocked by fibrin or blood. In one eye an iridectomy as well as two cyclodialyses were performed after extraction of the pseudophakos to reduce the intraocular pressure. However, the eye was ultimately enucleated due to pain and corneal dystrophy. An anterior vitrectomy was done in one eye after the clip lens was removed. In one eye puncture of the anterior chamber was performed because of haemorrhage. Resuturing of the corneal wound was done in one eye.

Table IV

2 reoperations performed on 19 eyes, three of which were reoperated on twice and one several times

Removal of pseudophakos	[illegible]
Replacing of pseudophakos	1
Discission of secondary cataract	3
Synechiolysis	3
Peripheral iridectomy	7
Cyclodialysis	[illegible]
Enucleation	1
Anterior vitrectomy	1
Puncture of the anterior chamber	1
Resuture of the corneal wound	1

Visual acuity

Visual acuity with the clip lens in situ was evaluated in 193 eyes (Table V) in 7 eyes the lens was removed and in three eyes there was no information of postoperative visual acuity as the patients were referred to a medical ward Visual acuity of 6/12 or more was found in 108 eyes (56 %) The main causes for a visual acuity of less than 6/12 are listed in Table VI As can be seen the most common cause was central degeneration Other frequent reasons were opacities on the lens or in the pupil and corneal dystrophy

Table V

Postoperative corrected visual acuity in 193 eyes with the clip lens in situ (7 patients with removed clip lenses and three patients referred to a medical ward postoperatively are excluded)

> 6/9	57
6/12–6/9	51
6/24–< 6/12	37
6/60–< 6/24	14
< 6/60	34

Table VI

Main cause for visual acuity less than 6/12 in 85 eyes

Preexistent causes	
Central degeneration	39
Dementia	[illegible]
Hemianopsia	1
Atrophy of the papilla	1
Postoperative causes	
Opacities on the clip lens or in the pupil	17
Corneal dystrophy	9
Macular oedema	2
Late recurrent hyphaema	1
Uveitis	1
Corpus opacities	1
Cause unknown	11

Discussion

Evaluation of the present series of 203 iris clip lens implantations performed in four Danish eye departments must be concerned with the complications following the implantation and the visual acuity obtained to determine whether it is justified to continue with the operation. A comparison is also made with conventional cataract extraction as well as with other pseudophakos implantations. However, as this is a retrospective study of a small number of operations it must be realised that this is just a comparison.

Seedorff & Lawetz (1969) evaluated the results of cryoextraction of cataract in 418 patients, of which 284 had uncomplicated cataract. As the population in the two series is nearly the same, it seems justifiable to compare the results as no proper control group exists. Regarding the more serious complications such as uveitis (17/203–33/284) and secondary glaucoma (2/203–4/284) the frequencies are seen to be equal in the two materials. Shallowing of the anterior chamber is seen twice as often in the present material (27/203–14/284) and corneal dystrophy is found only in the present series. A final visual acuity of 6/12 or above is more frequently found with conventional cataract extraction (56 %, 69 %), but the image is magnified by the aphakic correction.

Compiled studies of results obtained from implantation of a pseudophakos are presented by Duffner et al. (1976) who reported on 623 implantations of the iris plane Copeland lens performed in Miami, and Nordlohne (1975) who surveyed the results of lens implantation in the Netherlands (the results of approximately 2379 implantations of iris clip lenses performed by Dutch ophthalmologists). When the present material is compared to that of Duffner, uveitis (17/203–54/623), corneal dystrophy (13/203–45/623), secondary glaucoma (2/203–14/623) and opacities on the lens or within the pupil (18/203–38/623) are seen to lie within the same order of frequencies. Dislocation of the pseudophakos (6/203–6/623) seemed more frequent in the present material; the number of lenses removed (7/203–26/623) were of the same order. No eyes were enucleated in the Miami series; retinal detachment occurred in six eyes, whereas this was not observed in the present series. Visual acuity of 6/12 or more was found in almost the same percentages of cases (56 %–63.5 %). In the Dutch series dislocation of the lens was as frequent as in the present series (6/203–99/2379), corneal dystrophy was half as frequent (13/203–85/2379) and fewer clip lenses were removed. Enucleation was necessary in two cases. The visual acuity was better in the Dutch series and 76 % had a visual acuity of 6/12 or above compared to 56 % in the present series, but a lower mean age might be a reason for this.

In spite of the complications and the slight reduction in visual acuity in the present series it is considered justifiable to continue with implantation of iris clip lenses in elderly people in order to relieve them of the optical problems associated with aphakia

References

Duffner L R Wallace W K & Stiles W H (1976) The Miami cooperative community study on the Copeland intraocular lens (Pseudophakos) *Amer J Ophthal 82* 590–593

Nordlohne M E (1975) *The intraocular implant lens* Chapter VII 2nd ed W Junk B V The Hague

Seedorff H H & Lawætz B (1969) Intracapsular cataract extraction by the cryo technique and other methods *Acta ophthal (Kbh) 47* 761–773

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CONGENITAL GLAUCOMA BEFORE AND AFTER THE INTRODUCTION OF MICROSURGERY

Results of "Macrosurgery" 1943–1963 and of Microsurgery (Trabeculotomy/ectomy) 1970–1974

BY

E. GREGERSEN and SV. V. KESSING

Primary trabeculotomy (in five eyes converted to trabeculectomy) normalized the tension in all 21 eyes with congenital glaucoma without associated diseases (mean postoperative tension 12 mmHg, range 8–20 mm). Re-operation was needed for only one eye.
Preoperatively glaucomatous cupping was present in 18 of these 21 eyes. Ten of the 18 eyes with glaucomatous cupping were operated upon before the age of 6 months, two before 11 months, and the appearance of the disc was normalized in these 12 eyes.
Repeated trabeculotomy/ectomy was without success in three of five operated eyes in patients with congenital glaucoma of several years duration previously treated by "macrosurgery". In patients with associated diseases normal tension was achieved by means of trabeculotomy/ectomy in two eyes in two Sturge-Weber children with unilateral congenital glaucoma and in both eyes in a child with a chromosomal defect with bilateral congenital glaucoma. Repeated trabeculotomy/ectomy was on the other hand without success in a child with bilateral aniridia with congenital glaucoma and hydrocephalus.

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Presupposing acute or subacute microsurgery the present operative results *of congenital glaucoma without associated diseases are far better than those* obtained in previous decades by macrosurgery which despite frequent re operations effected normalization of the tension in only 61 % of the eyes (11 of 26 patients (42 %) with bilateral congenital glaucoma without associated diseases and treated by macrosurgery in previous decades were *under the Care of the Blind)*

Key words congenital glaucoma – previous macrosurgery – present microsurgery – trabeculotomy – trabeculectomy

This account is intended to report the results of treating congenital glaucoma by previous decades macrosurgical and the present microsurgical methods

Incidence of congenital glaucoma in Denmark

The incidence of congenital glaucoma in Denmark was established by Erik Westerlund in 1947 During a 20 year period (1921–1940) 44 cases were recorded among 548 142 live born infants i e an incidence of 0 008 % (± 0 0012 %) It was stated that during the period 1931–1940 with a mean of 66 200 live births per annum this would correspond to 4–6 new cases annually As the present number of live births is about 70 000 per annum about six cases have to be expected every year

Results of previous decades "macrosurgery

The results of surgical treatment of congenital glaucoma in Denmark before the microsurgical epoch have been well elucidated (Hans Walter Larsen 1968) This macrosurgical material represents all cases of buphthalmos admitted to the University Eye Clinic Copenhagen during the period 1943–1963 It comprises 32 patients with bilateral and 10 with unilateral congenital glaucoma without associated diseases as such patients were excluded Twenty nine of the bilateral and all the unilateral cases were subjected to operation (a total of 110 operations on 53 eyes in the bilateral group and 16 operations on 10 eyes in the unilateral group) The operations performed were goniotomy Elliott s *trephining cyclodiathermy and cyclodialysis in that order of frequency*

Twenty six patients of the bilateral group and nine of the unilateral group were seen at follow up after a mean of 11–14 years Within the bilateral group tension proved to be normal in 30 of 49 operated eyes (61 %) In 23 of 49 eyes (47 %) of this group the visual acuity was better than 6 60 in 15 of 49

Table I
Macrosurgical cases of congenital glaucoma 1945–1963
(Follow up period 11–14 years)

49 eyes in 26 bilateral cases
9 eyes in 9 unilateral cases
(surgery: goniotomy, trephining, diathermy, cyclodialysis)
Bilateral cases: 61 % normotensive eyes (30 of 49)
vision > 6/60 in 23 of 49 eyes (47 %), ≥ 6/18 in 15 of 49 eyes (31 %)
Unilateral cases: Poorer results of operated eyes
(Hans Walther Larsen 1968)

eyes (31 %) ≥ 6/18. Eleven of the 26 bilateral patients were under the Care of the Blind. In the unilateral group the operated buphthalmic eye showed a poorer prognosis than in the bilateral group. (It may be mentioned that in four eyes of the bilateral group the tension had spontaneously become normal.)

Present (Microsurgical) Material

Composition

Congenital glaucoma is taken to mean here glaucoma which has entailed an increased corneal diameter or suspicion thereof, i. e. a diameter > 11.5 mm (Kolker & Hetherington 1970). The material comprises all patients with congenital glaucoma received for treatment in the University Eye Clinic, Copenhagen, during the period 1970–1974 (microsurgery on the trabecular meshwork having been introduced in the Clinic in 1970).

Out of a total of 21 patients, 17 were boys (two of the "boys", however, now being 28 and 34 years of age) and four girls. Sixteen had bilateral and five unilateral congenital glaucoma, which gives a total of 37 eyes with congenital glaucoma. Sixteen of the 21 patients were new cases from the 5 year period under consideration. Thus the material represents about half the expected new cases in Denmark. In 1973 P. M. Møller reported the results in another Danish series treated by goniotomy as the preferred microsurgical method.

Of the 37 eyes with congenital glaucoma, 31 eyes in 17 patients could be classified as congenital glaucoma without associated diseases, whereas in six eyes of four patients there were associated diseases (Sturge-Weber in two unilateral cases, aniridia in one bilateral case, and chromosomal defect with multiple malformations in one bilateral case (Table II). Trabecular operations

Table II
Microsurgical cases of congenital glaucoma 1970–1974

32 eyes in 16 bilateral cases (12 ♂ and 4 ♀)
(14 patients without assoc diseases)
(1 patient with chromosomal anomaly)
(1 patient with bilateral aniridia)
5 eyes in 5 unilateral patients (5 ♂)
(3 patients without assoc diseases)
(2 patients with Sturge Weber s disease)
(5 unoperated blind eyes)

were performed on 32 of the 37 eyes (not on five eyes because of absent perception of light after previous macrosurgery)

Intraocular tension was measured on the first occasion under intubation anaesthesia using cyclopropane At the repeated follow up examinations after surgical treatment the measurements were carried out under superficial halothane anaesthesia without intubation but with spontaneous natural respiration to avoid the hypotensive action of deep anaesthesia and hyperventilation The measurements were performed with Draeger s as well as with Perkins applanation tonometers

Preoperative state (32 eyes in 21 patients undergoing trabecular surgery)

The diagnosis of congenital glaucoma had been made usually around the age of one year (in half the cases at 6 months or earlier range 3 weeks 4 years) Preoperative tension was $>$ 30 mmHg in 23 ey[illegible] and $<$ 30 mm in nine In

Table III
Preoperative findings in the microsurgical material

32 eyes in [illegible] patients
Age at diagnosis 3 weeks – 48 months $<$ 6 months in 10 pts
Preoperative tension $>$ 30 mm in [illegible] eyes 15–30 mm in 9 eyes
Corneal diameter 13–15 mm in 31 eyes 12 mm in 1 eye
Corneal oedema and/or tears in Descemet s membrane in 30 eyes
Glaucomatous cupping of the disc in 25 eyes
(5 discs normal 2 unassessable)

Table II

Microsurgical type a (primary microsurgery primary congenital glaucoma)

21 eyes in 13 patients
17 trabeculotomies 5 trabeculectomies
Postoperative tension normal in all eyes
Glaucomatous cupping cured in 12 of 18 eyes
Age at operation < 8 months with cured cupping in 10 eyes
Mean follow up period 3 years

Tension at follow up

Tension became normal i e mean 12 mm (range 8–20 mm) without medication in all 21 eyes with congenital glaucoma without associated diseases and with primary microsurgery (type a) Re operation was needed for only one eye (Preoperative mean tension in this group 31 mm)

Among the remaining 11 eyes (types b c and d) treated by microsurgery only six obtained a normal tension In five eyes it could not be controlled (two eyes with congenital glaucoma plus associated diseases and three eyes with primary congenital glaucoma in patients over 10 years of age who had a previous history of macrosurgery)

Incidentally the results in the various surgical types are set out in Tables IV–VII)

Cornea at follow up

In 27 of the 32 eyes the cornea was without any oedema viz the 27 eyes in which a normal tension was obtained The corneal diameter was unchanged

Table V

Microsurgical type b (secondary microsurgery primary congenital glaucoma)

5 eyes in 4 patients
1 trabeculotomy 8 trabeculectomies
Tension normal in 2 eyes
Glaucomatous cupping unchanged

Discussion

The most striking results were obtained in the group of 21 eyes with congenital glaucoma without associated diseases who underwent primary microsurgery Within this group tension was normalized (Grote 1975) in all eyes (only one eye needing re operation) and glaucomatous cupping of the disc disappeared postoperatively in 12 eyes (cf Kessing & Gregersen 1977)

Owing to the young age of the children it is not possible to decide whether the transient preoperative glaucomatous cupping of the disc will affect vision even though the discs now appear normal It must be mentioned that in the case of the 12 eyes which postoperatively showed normalization of the disc all the patients underwent the operation before the age of 6 months except one patient operated at 11 months of age The six patients of this group in whom the disc was not normalized had a mean age of 8 years (range 1–12 years) at the time of operation

The very favourable surgical results in patients with primary (simple) congenital glaucoma undergoing primary microsurgery agree with those reported by Harms & Dannheim (1969) who obtained a 100 % normalization of tension in their group of 18 eyes with primary congenital glaucoma undergoing primary trabeculotomy during the first year of life

The use of the U probe without a handle has in our hands been an excellent way to determine in which patients an intended trabeculotomy had to be converted to trabeculectomy that is when pushing the U probe with a chalazion spoon revealed firm resistance to probing

Early and primary trabeculotomy (if necessary converted to trabeculectomy) for uncomplicated congenital glaucoma also appears to have the great advantage that re operation is more rarely needed than after the use of other surgical methods such as goniotomy and goniolysis (Sautter & Lerche 1968 P M Moller 1973 d Epinay 1975)

Only one eye (in a patient with Sturge Weber s disease) developed a serious complication i e inflammation and phthisis about 6 months after the operations (1 trabeculotomy and 1 trabeculectomy on the same eye)

In the small number of eyes where microsurgery was performed secondary to other treatment the results were poor presumably because previous macro surgery or further enlargement of the eye during time elapsed had caused collapse or obstruction of Schlemm s canal Moreover previous cyclodiathermy had left the conjunctiva and sclera with large perilimbal scars which meant that both trabeculotomy and trabeculectomy had a poor prognosis

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THE DISTENDED DISC IN EARLY STAGES OF CONGENITAL GLAUCOMA

BY

SV V KESSING and E. GREGERSEN

In 1? out of 18 eyes operated upon for congenital glaucoma without asso ciated diseases the preoperative glaucomatous cupping had disappeared at follow up 2 weeks to 3 months after the operation (trabeculotomy ab externo on 9 eyes and trabeculectomy on 3 eyes) Of the 12 eyes 10 had had the operation performed before the age of [illegible] months in contrast to the group in which glaucomatous cupping of the disc was irreversible where operation had been performed in the age range 6 months – 1? years (mean 6 years)
The mean postoperative tension value in the 18 eyes was 1? mm (range 8–?0 mm) without medication mean observation time 3 years
It seems likely that during the first phases of congenital glaucoma the disc is distended i e of increased diameter and depth This form of glaucomatous cupping and the increased diameter of the disc may be due to pressure conditioned enlargement of the scleral canal and omnidirectional distention of the lamina cribrosa This distention manifests itself mainly in the central areas of the lamina cribrosa and the disc and usually disappears when the tension is normalized by surgery during the first phases of the disease

Key words congenital glaucoma – glaucomatous cupping of the disc – distention of the scleral canal lamina cribrosa and disc – postoperative normalization

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The object of the present publication is to describe the pre- and post-operative findings regarding the disc in a group of children with congenital glaucoma without associated diseases where the sole form of treatment was trabeculotomy/ectomy.

Material

The material comprises 21 eyes in 13 successive children with primary congenital glaucoma admitted to the Clinic during the period 1970–1974. The mean age was 3 years, range 2–144 months. No child had undergone surgical treatment prior to admission (cf. also Gregersen & Kessing 1977).

Preoperative findings (tension, cornea and disc)

The mean preoperative tension was 31 mmHg, range 15–52 mm, measured with an applanation tonometer under general cyclopropane anaesthesia with intubation. The corneal diameter ranged from 13 to 15 mm (15 mm in 8 eyes) and in all the children the cornea exhibited oedema or tears in Descemet's membrane.

Eighteen of the 21 eyes exhibited glaucomatous cupping of the disc, defined as cupping comprising about half or more of the disc diameter in one or more meridian. In three eyes the discs were normal.

Surgery and postoperative tension

Trabeculotomy ab externo with a U probe was intended in all 21 eyes but was accomplished in only 16. In five instances it proved impossible to probe Schlemm's canal and the planned trabeculotomy was therefore converted into trabeculectomy. After the operation the tension returned to normal in all 21 eyes without medication (mean postoperative tension 12 mm, range 5–20 mm). The postoperative follow-up examinations were performed every 3 months under halothane anaesthesia without intubation, i.e. with spontaneous and natural respiration to avoid the pressure reducing effect of deep anaesthesia and low blood pressure, mean observation time 3 years (range 1–6 years).

Re-operation was needed in only one case (re-trabeculotomy on one eye).

Postoperative changes of the disc

In 12 out of the 18 eyes with glaucomatous cupping follow-up 2 weeks to 3 months after the operation showed a normal appearance of the previously glaucomatously cupped disc (cf. Fig. 1). Here a normal cupping (physiological

Fig 1

(a) Disc during preoperative hypertensive phase

(b) The same disc during postoperative normotensive phase

On the preoperative photograph the glaucomatous cupping in the hypertensive phase occupies about 2/3 of the d sc diameter in the vertical meridian At the same time the vessels are slightly displaced and kinked at the upper and lower borders of the cupping On the postoperative photograph the cupping occupies only about 1/6 of the disc diameter and the vascular displacement and kinking have disappeared indicating reduced or abolished distention of the scleral canal and reduced or abolished distention/ posterior displacement of the lamina cribrosa and disc tissue.
Comparison of the preoperative and postoperative photographs also suggests that during the preoperative hypertensive phase the disc is 10– 0 % larger than in the postoperative normotensive situation This difference in size is presumably attributable to an increased diameter of the scleral canal as well as to papilloedema during the hypertensive phase (A photographic element in the size difference can probably not entirely be ruled out but this is believed to be of very slight extent judging by the calibre of arterioles and venules in the two photographs)
(The photographs are from a patient operated upon at the age of 5–6 months The preoperative photograph was taken immediately prior to the operation when the tension had been measured as 30 mm under general cyclopropane anaesthesia Ophthalmoscopy six weeks after the operation showed a normal disc exactly as seen on the postoperative photograph taken five months after the operation)

excavation) is defined as cupping < 1/3 of the disc diameter in all meridians (cf. Richardson 1968*).

All patients (except one) who had a normal disc postoperatively had had the operation performed during the first 6 months of life and all had a corneal diameter of 13–15 mm (15 mm in 5 eyes). The remaining six patients who had irreversible glaucomatous cupping underwent operation in the age range 6–144 months (mean age at operation 6 years).

Discussion

Disappearance of glaucomatous cupping in congenital glaucoma was reported as early as 1965 by Chandler & Grant, in 1966 by Lister, and has later been confirmed by J. Hetherington (1968), Schaffer & Hetherington (1969) and Anderson (1975).

This normalization of the disc may be interpreted by assuming that the preoperative cupping is due to posterior and transverse distension and displacement of the lamina cribrosa and disc tissue, more pronounced centrally than in the periphery of the lamina and the disc. Thus Anderson (1975) has suggested that the mechanism of normalization may be a reduction in the diameter of the scleral canal with less posterior bulging of the lamina cribrosa after the tension has been lowered surgically. This theory also indicates a postoperative *reduction of the disc diameter*.

Schaffer & Hetherington (1969) on the other hand suggested the "astroglia hypothesis" to explain the normalization of the glaucomatous cupping.

Since the normalization of the glaucomatous cupping in the present series was observed from 2 weeks to 3 months after the operation, we feel that cured distention of the scleral canal, lamina cribrosa and disc tissue is more likely than newformation of glial tissue.

In relation to the above described distension concept it may be mentioned that in 9 of the 12 eyes with postoperative normalization of the disc a reduction of the cornea diameter from 15 to 14 mm was recorded.

As tension measurements under general anaesthesia are to some extent affected by the anaesthesia, *postoperative checking* of the appearance of the disc is an extremely important factor in the assessment of the sufficiency of the operation and the prognostic outlook.

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*) Richardson found cupping that exceeded 1/3 disc diameter in only [illegible]6 of 936 eyes in 468 normal newborns, i.e. in 2.6 % of the eyes.

Acknowledgment

is paid to Anders Vilhelm Jørgensen's fond for research in glaucoma.

References

Anderson D R (1975) *Glaucomatous disc changes in infants* Transactions of the New Orleans Academy of Ophthalmology pp 104–105 The C V Mosby Company Saint Louis

Chandler P A & Grant W M (1965) *Lectures on Glaucoma* p 327 Lea & Fibiger Philadelphia

Gregersen E & Kessing Sv V (1977) Congenital Glaucoma Before and After the Introduction of Microsurgery *Acta ophthal (Kbh)* 55 422–430

Hetherington J (1968) Discussion of paper on Optic Cup Symmetry in Normal Newborn Infants by Kenneth T Richardson *Invest Ophthal* 7 140

Lister A (1966) The Prognosis in Congenital Glaucoma *Trans ophthal Soc U K* 86 5

Richardson K T (1968) Optic cup symmetry in normal newborn infants *Invest Ophthal* 7 137–140

Shaffer R N & Hetherington J (1969) The glaucomatous disc in infants *Trans amer Acad Ophthal Otolaryng* 73 929–935 (presented 1968)

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GONIOTOMY AND CONGENITAL GLAUCOMA

BY

P. M. MØLLER

A survey is presented of the operative results obtained in 45 eyes suffering from congenital glaucoma, primarily operated on using micro-surgical techniques: either goniotomy as described by Worst, or trabeculotomy. Thirty-eight of the 45 eyes have, during an observation period of 1-10 years (average 5.5 years), a normal pressure of less than or equal to 18 mmHg measured using Draeger's technique. A relatively high frequency of recurrence has been found following an average observation period of 3.5 years in patients who were primarily normalized by Worst's goniotomy.

Key words: congenital glaucoma – Worst's goniotomy – pressure control during anaesthesia – recurrence frequency.

We have in the University Eye Clinic in Odense been particularly interested in the treatment of congenital glaucoma for the last 10 years. The introduction by the Dutchman J. C. F. Worst of microsurgical goniotomy (Worst 1963) stimulated this particular interest.

A short report of our preliminary results was published after the first six years (P. M. Møller 1973).

Material and Methods

Over a ten year period 1965–1975 a total of 41 patients have been admitted to the Ophthalmological Department of the Odense University Hospital suffering from congenital glaucoma There were 27 males and 14 females 9 were unilateral cases and 32 patients had bilateral glaucoma we have thus had during the period 73 eyes with congenital glaucoma The present paper will be mainly concerned with 41 of these 73 eyes which were primarily treated with goniotomy as described by Worst In two patients a total of four eyes our primary operation was trabeculotomy thus 45 eyes were treated from the age of 3 days to 3 years

The present author has studied the technique of goniotomy from 1964 to 1970 at the Clinic of Worst in Groningen Our initial procedure has therefore been goniotomy performed under a microscope with Worst s hydrostatic anterior chamber needle The patients have been subjected to examination under general anaesthesia in connection with the first operation.

The procedure at the primary examination involved measurement of the corneal diameter and inspection with regard to corneal opacities and tears in Descemet s membrane Ophthalmoscopy and measurement of the intra ocular pressure were carried out, and lastly the goniotomy was performed The intra ocular pressure was measured in all the cases using an applanation tonometer as described by Draeger All the patients were examined under trilene anaesthesia We have as other authors (Hetherington & Schaffer 1968) been somewhat dubious regarding the pressures measured in the eye under anaesthesia Our experience suggests that patients under deep surgical anaesthesia have a falling pressure in relation to the pressure measured immediately after the induction Therefore we have made it our routine to measure the pressure under trilene anaesthesia as we have noted that the tension at this time and during this anaesthesia lies nearer the actual value than that measured following prolonged fluothane anaesthesia Thus on numerous occasions we have alternated between trilene anaesthesia and fluothane and have always found that the pressures measured during prolonged fluothane anaesthesia were lower than those during trilene anaesthesia The fall in pressure has on average been between approximately 5 and 8 mmHg

The procedure followed was exactly as described by Worst (Worst 1966) The average period of hospitalization in connection with goniotomy was one week After this the patients were anaesthetized with trilene and the pressure measured If the pressure was found to be within normal range – we consider 18 mmHg to be the maximum permissible – the patient was sent home without any additional treatment They have always been re admitted at a later date

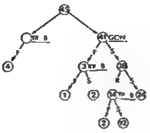
We have always followed up our patients at close intervals. After the first operation the patient was hospitalized 3 months later and thereafter at intervals of 6 months, 9 months and one year. Thus we have seen our patients approximately 8 times up to the age of 4 years. After this age we have generally been able to control the patients without the use of anaesthesia approximately once a year.

Results

The results of goniotomy according to the method of Worst as the initial operation on a total of 41 eyes are shown in Table I. The observation time was one to 10 years, average 5.5 years. The primary results were good. We were primarily able to regulate the pressure to less than 18 mmHg in 38 of the 41 eyes. We were unable to control the pressure initially in three eyes. A total of 56 operations (Worst) were carried out on these 41 eyes. The great majority of patients were subjected to one goniotomy, a few patients to two and very few to three on both eyes. On average we carried out less than one and a half operations on each eye. Of the 38 eyes that were primarily regulated it was necessary to re-operate on 14. We found during repeated re-admissions and control that an increase in intra-ocular pressure re-appeared in these eyes after an interval of 6 months to 5 years, on average 3½ years, in spite of the fact that the primary operation had given good results. Trabeculotomy has been the second operation in all the cases where this was required; an additional trabeculectomy has been necessary in a very few cases. In the few patients (2) who were subjected to three goniotomies on each eye we were thus able to control the pressure and reduce it to within normal range for a period of from 3 to 5 years before it became necessary to re-operate. We were only unsuccessful in controlling the pressure by re-operation in two eyes. In three patients in whom it was not possible to control the pressure initially, it was necessary to perform trabeculotomy and among these three patients we were unsuccessful in regulating the pressure in one case.

Summarizing, we were able to regulate the pressure by goniotomy or goniotomy plus trabeculotomy in a total of 38 eyes, whereas we were unable in three eyes to regulate the pressure despite combined operations. In four eyes we were unsuccessful in regulating the pressure despite numerous trabeculotomies and trabeculectomies. The operations were carried out as primary procedures without first performing a goniotomy. These four eyes differ from the remainder of the group in that they presented symptoms immediately after birth.

45 eyes with congenital glaucoma
subjected to microsurgery



T B TR BECULO OMY
GON. GON O OMY
S SUCCES
R RECURRENCE
F F LU E

SUCCES 38

F LU E 7

Table I

Goniotomy and congenital glaucoma. Results of surgery

These four eyes in two girls were admitted to the department at an interval of one month with dense corneal opacities observed immediately after birth We started treatment of both girls with a trabeculotomy which presented no problems and a clearer cornea together with a pressure within normal range was obtained in all 4 eyes However within a few days the pressure again rose and several operations were carried out during the ensuing year on both children Partly as mentioned, trabeculotomies which were repeated and partly trabeculectomies but at no time were we successful in regulating the pressure The patients did not become symptom free until after the use of cyclocryothermy at approximately 9 months of age We have now followed up these children for one year and the pressure is within normal limits though it has been necessary to medicate them with acetazolamide (Diamox®) in order to attain this They still have dense corneal opacities and a visual acuity corresponding to hand movements

Summarizing (see (Table I) it can be said that out of a total of 45 eyes we have been able to regulate the pressure partly by means of goniotomy and partly with trabeculotomy/trabeculectomy in 38 eyes whereas we have been unsuccessful in regulating the pressure in the usual way in the remaining seven eyes

Discussion

We will return to the seven eyes where we were unable to normalize the pressure These comprise as mentioned under methods four eyes in two girls with symptoms immediately after birth two eyes in a child with Lowe s

syndrome and one eye in a severely mentally deficient girl with severe Sturge Weber syndrome We consider as do other authors (Worst 1966) that patients with symptoms immediately after birth have a poor prognosis This was suggested by Worst in his monography from 1966 He mentioned several patients with symptoms immediately after birth with corneal opacities where despite several goniotomies he was unable to regulate the pressure

We were able to regulate the pressure in three patients with Sturge Weber syndrome and unilateral glaucoma as well as in two mongol children with in one case unilateral and in the other bilateral glaucoma This was done partly by means of goniotomy and partly by a combination of operations We do not therefore consider it necessary to divide the children into groups with and without defects in addition to their glaucoma This thus naturally gives rise to the grouping between the late advanced and early advanced congenital glaucoma The basic idea in Worst s thesis is that the chronological age of congenital glaucoma is quite different from the developmental age Children who are born with very evident congenital glaucoma have an early onset of the disease during intrauterine life at a stage where the eye is still underdeveloped Congenital glaucoma stops the development of the eye If the eye has almost completely developed then the onset of congenital glaucoma is treatable by goniotomy as this is a physiological type of operation If the intrauterine onset is earlier then not much can be done as the chamber angle structures have not developed sufficiently enough to function

If one has worked with goniotomy according to the method described by Worst for 10 years then one can in the majority of cases during micro surgical procedures find the physiological background of the congenital glaucoma Severing of an obvious Barkan s membrane with an immediate downward movement of the iris root and the appearance of Schlemm s canal convinces one of the accuracy of Worst s theory This observation of a Barkan s membrane and the severing of the same has nothing to do with any other defects of the patient such cases can be collectively tabulated in the group late developed congenital glaucoma in contrast to the early onset of glaucoma at a stage when the eye is still severely underdeveloped

Our two patients with severe symptoms immediately after birth were primarily operated on with a trabeculotomy This was almost certainly an incorrect operation at that time The structures of the chamber angle which could not be observed owing to the corneal opacities could not be made to function despite an apparently successful trabeculotomy A primary trabeculectomy would probably have been a more correct operation However even a trabeculectomy immediately after the unsuccessful trabeculotomy could not reduce the pressure to normal values The narrow anterior chamber with the anteriorly

displaced lens and elongated zonular fibres together with high intraocular pressure caused immediate prolapse of the vitreous body into the anterior chamber following even minor surgery on the iris with deleterious results for two of the operated eyes

If we now return to our results with the primary Worst s goniotomy one will immediately note the large number of recurrences within the course of 3 to 5 years

Our frequency of recurrence is higher than that stated by other authors Thus Hass (1968) states that he had a frequency of recurrence after one year of observation of 18 per cent following a successful goniotomy as described by Barkan

The number of recurrences in our material after an average observation time of 3 5 years is 14 out of 41 (34 %) Sautter & Lerche (1974) make no mention of their frequency of recurrence during an observation period with 87 eyes operated on according to Barkan In these cases the observation time for more than half of the patients was more than 2 years The immediate impression is that our frequency of recurrence is high whereas our final results with control of the pressure to normal values in our micro-surgically operated glaucoma material are satisfactory in 38 out of 45 operated eyes

A more thorough comparison of the results obtained by goniotomy as described by Worst and by Barkan and the results obtained by external trabeculotomy are hardly permissible the first five years Sautter & Lerche (1974) found by comparing goniotomy as described by Barkan with trabeculotomy and using an observation period of up to 2½ years that a decisive difference between the results was not evident

We have only had very few and slight complications in connection with our goniotomies according to the method of Worst A later evaluation of the patients treated for congenital glaucoma using various operative methods will determine whether goniotomy or external trabeculotomy is the better method In this connection the most important aspect is the occurrence of secondary cataract in patients in whom a normal pressure is obtained

There is little doubt that very few goniotomies either according to the method of Barkan or Worst will be carried out in the future The continued use of Worst s operation will be confined to the departments where this operation has become a speciality Worst s operation is time consuming and considerably more difficult than external trabeculotomy If one has the experience in operating under the microscope the performing of a trabeculotomy where Schlemm s canal is present is a rapid and easy operation Thus in all our operations carried out owing to recurrence and where we have preferred trabeculotomy we have been able to find a functioning Schlemm s canal

An earlier attempt at centralizing the treatment of congenital glaucoma here in Denmark, where there are no more than six new cases per year, has not been successful. It is surprising, after having had many years experience in the treatment of congenital glaucoma, that so few authors mention Worst's genial operative method with a hydrostatic anterior chamber needle, and that so few authors refer to this unique work on the development of the chamber angle and the pathophysiological causes of congenital glaucoma.

References

Haas, J. (1968) Principles and problems of therapy in congenital glaucoma. *Invest. Ophthal.* 140–146.

Hetherington, J., Jr. & Schaffer, R. N. (1968) Tonometry and tonography in congenital glaucoma. *Invest. Ophthal.* 7, 134–13[illegible].

Møller, P. M. (19[illegible]3) Goniotomy in congenital glaucoma. *Acta ophthal. (Kbh.) Suppl.* 1[illegible]3, 1[illegible]5–1[illegible].

Sautter, H. & Lerche, W. (1974) Neuere Verfahren zur operativen Behandlung des angeborenen Glaukoms. *Münch. med. Wschr.* [illegible], 1833–1838.

Worst, J. G. F. (1963) An improved method for chamber angle surgery in congenital glaucoma. *Ann. Instit. Barraquer* 4, [illegible]3–3[illegible]0.

Worst, J. G. F. (1966) *The pathogenesis of congenital glaucoma.* Charles C. Thomas, Publisher.

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VARIATION AND HERITABILITY OF OCULAR DIMENSIONS
A Population Study among Adult Greenland Eskimos

BY

P H ALSBIRK

Adult Greenland Eskimos from Umanaq town (age 15+) and villages (age 40+) were examined Optical pachymetry ultrasonic oculometry corneal diameter and curvature measurements and subjective refraction were performed in 5–600 persons Frequent occurrence of primary angle closure glaucoma motivated the survey

Age sex and family variations were studied by linear regression analyses Conspicuous age effect was found with respect to increase of lens thickness and forward displacement of the lens with age Almost no age influence was found with respect to corneoscleral size i e axial length corneal size and corneal radius of curvature Conspicuous heritability ($h = 0.6–0.8$) was found in corneoscleral size parameters as well as lens position while refractive error showed a much smaller genetic influence

Key words corneal diameter – corneal thickness – corneal curvature – anterior chamber depth – lens thickness – lens position – vitreous body – axial length – refraction – age/sex variation – polygenic inheritance – heritability – Greenland Eskimos

The recent development of optic and ultrasonographic methods has greatly benefitted oculometric research However there are still many unsolved problems of relevance to various diseases and refraction among these the relative influence of genetic and environmental factors on ocular anatomy

Population studies among Eskimos in Alaska Canada and Greenland have recently contributed to the current oculometric discussions In Alaska and

Canada an *epidemic of myopia* in adolescents has appeared through the last 20 years (Young et al 1969, 1972; Morgan et al 1973, 1975). So far similar observations have not been made in Greenland (Skeller 1954; Alsbirk & Forsius 1973). On the other hand an *epidemic of primary angle closure glaucoma* (*a.c.g.*) apparently occurred in Greenland in the 1960-ies (Clemmesen & Alsbirk 1969). Epidemiological studies showed that a.c.g. is about 40 times more prevalent in Eskimos from Canada and Greenland than in Caucasians (Drance 1973; Alsbirk 1975a). Oculometric studies revealed that a shallow anterior chamber in Eskimos is an important characteristic of this ethnic group (Clemmesen & Alsbirk 1971; Drance et al 1973; Alsbirk & Forsius 1973; Alsbirk 1974b).

The present paper describes the age-, sex- and family variations of ocular dimensions and refractive error based on a general population study of about 500 adult Greenland Eskimos.

Material and Methods

The native population of Umanaq district in West Greenland formed the basis of the investigation. With a 95% participation rate in preselected groups a pachymetric anterior chamber depth survey was performed in 1969. Altogether 981 persons were examined, i.e. 661 town inhabitants above 7 years and 2 0 persons in the 8 villages aged 40 years or more (Alsbirk 1974a). The adults (above 15 years) from this basic material were further examined in 1971 and 1972 as shown in Table I. In the refraction survey 1972 one village (Satut) had to be excluded (due to lack of time during a 4 weeks' visit to the district).

In Tables II-IV the *interpersonal variation* is described using the average of both eyes of each person (i.e. uniocularly measured persones were excluded). The loss from Table I to following tables was due to various impeding conditions, mostly monocular. The largest deficit comprised 50-53 persons who could not be reliably refracted in both eyes, mostly due to poor visual acuity or bad cooperation. In the family correlation study uniocular measurements were taken to represent the individual when values from both eyes were not available.

Anterior chamber depth (*ACD*) and *corneal thickness* (*CT*) were optically measured in 1969 using Haag-Streit 900 pachymetry (Lowe 1966; Alsbirk 1974c). Concomitantly *corneal diameter* (*CD*) was measured transversally and vertically using Wessely's keratometer (Wessely 1911; Alsbirk 1975c).

The *ultrasonic oculometry survey* performed in 1971 used a transportable Smith-Kline ophthalmic ultrasonoscope Ekoline 12 with a plane 5 mm 7.5 MHz transducer. A 12 mm wide contact glass was used, similar to that of Jansson (1963), giving a 3-4 mm methocel column between the transducer and cornea. No cycloplegics were used. A polaroid photo was generally taken of both eyes of each person. The ocular distances were read with loupe from these photos to 0.1 mm values. Subsequently the correction factors necessitated by different sound velocities in aqueous (0.993), lens (1.064) and vitreous (0.935) were determined using an interferometer with distilled

water cf the methodological survey by Fledelius (1976). In this way the *anterior chamber depth including corneal thickness* ACD_u was determined in the supine person. Furthermore *lens thickness* LT, axial length of *vitreous body* VB and total *axial length* AL were obtained. No correction for retinal thickness was added.

The *refraction survey* in 1972 comprised measurement of *corneal power* CP in two meridians using a Javal Schiøtz keratometer. Visual acuity was determined without and with the subjectively preferable correction in front of Snellen's chart at 6 metres. These results were transformed into *radius of corneal curvature* CP *(= 337.5/CP) and into refractive error* PF both based on *spherical equivalents* when any astigmatism was present in CP or at the refraction respectively.

By repeated measurement a few weeks later of a randomly selected subsample (29 persons in Umanaq) the *precision* was examined. The following ultrasonic *errors of measurement* were found, given as standard deviations (in mm and per cent of the average value): ACD 0.10 mm = 3.1 %, LT 0.12 mm = 2.8 %, VB 0.21 mm = 1.3 %, AL 0.26 mm = 1.1 %. Correspondingly the optical measurements had been controlled: ACD 0.037 mm = 1.4 %, CT 0.013 mm = 2.5 %, CD 0.18 mm = 1.6 % cf. Alsbirk (1974c, 1975c).

The ultrasound survey was started in collaboration with my ophthalmological consultant Viggo Clemmesen M.D. The refractions were made in cooperation with my wife *Ida Alsbirk who had some years' experience as a refractionist in Greenland*. Some of the CP determinations were made by a trained medical student. All other measurements were made by me.

Table 1

Material based on anterior chamber depth (ACD) sample from 1969. Participation and loss in ultrasound oculometry survey 1971 and refraction survey 1972 is specified.

	Ultrasound survey No. of persons	Refraction survey No. of persons
No. examined age 15+, total	616 = 82 %	533 = 74 %
Loss due to		
death or disease	16	33
removal or temporary absence	86	114
non appearance, refusal	31	40
Loss, total	133 = 18 %	187 = 26 %
Preselected material, total	749 = 100 %	720 = 100 %
Excluded due to		
age 7–14	182	156
location (village Satut)		55
ACD sample, total	931	931

Table II

Age variation and sex difference of [illegible] ocular dimensions and refractive error in adults above 15 years with both eyes measured

	No. and sex of persons examined	Age (x) $\bar{x}$	Ocular dimension (y) in mm					
			mean $\bar{y}$	standard deviation $s_{y \cdot x}$	regression coefficient b_{yx}	standard error s_b	mean at age [illegible]0	mean at age [illegible]0
Corneal diameter	[illegible]63 M	43.5	11.11	0.41	-0.00[illegible]6	0.0016	11.17	11.01
= CD	[illegible] F	43.[illegible]	10.90	0.41	-0.00[illegible]5	0.0015	10.96	10.84
Corneal thickness	291 M	4[illegible]	0.[illegible]1[illegible]	0.0[illegible]9	0.000[illegible]2 *	0.00010	0.5[illegible]6	0.495
= CT	344 F	41.8	0.[illegible]6	0.0[illegible]9	0.00016	0.00009	0.[illegible]9	0.5[illegible]1
Corneal radius	23[illegible] M	43.8	[illegible].85	0.23	0.[illegible]002	0.0009	7.84	[illegible].8[illegible]
= CR	2[illegible]6 F	43.3	[illegible]8	0.24	0.0006	0.0009	[illegible]9	[illegible].66
Anterior chamber depth (CT incl.)	2[illegible]9 M	4[illegible].8	3.24	0.35	0.0161*	0.0012	3.66	2.85
= ACD$_0$	3[illegible]0 F	44.6	3.06	0.36	0.01[illegible]3* *	0.0012	3.49	2.[illegible]3
Lens thickness	2[illegible]9 M	45.8	4.36	0.27	0.0[illegible]35	0.0010	3.[illegible]6	4.98
= LT	3[illegible]0 F	44.6	4.37	0.28	0.0[illegible]11 **	0.0010	3.8[illegible]	4.90
Vitreous body	[illegible]9 M	4[illegible].8	16.11	0.81	0.00[illegible]*	0.00[illegible]9	16.[illegible]8	15.94
= VB	3[illegible]0 F	44.6	1[illegible].57	0.[illegible]9	0.0105 *	0.00[illegible]8	15.83	15.30
Axial length	2[illegible]9 M	4[illegible].8	23.71	0.88	0.000[illegible]	0.0032	23.[illegible]9	23.73
= AL	3[illegible]0 F	44.6	23.00	0.8[illegible]	-0.006 *	0.0030	2[illegible].17	[illegible]2.83
Refractive error	2[illegible]2 M	4[illegible].6	-0.07	1.34	-0.001	0.006	+0.01	-0.18
= RF in diopters = D	261 F	42.3	+0.[illegible]	1.25	0.0[illegible]4* *	0.00[illegible]	-0.[illegible]8	+0.90

Sex difference between means CD CR ACD VB AL $P < 0.001$ M > F
CT $P < 0.001$ LT n.s. RF: $P < 0.01$ F > M

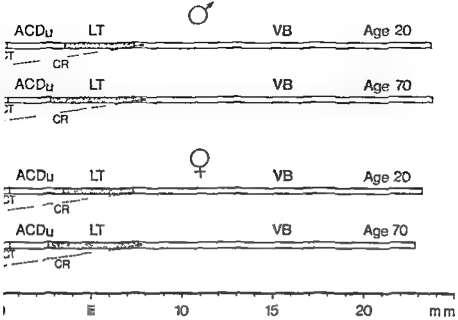

Fig 1

Ocular dimensions in adults aged 20 and 70 years calculated as in Table II The increase of lens thickness (LT) and forward displacement of the whole lens is seen, reducing anterior chamber depth (ACD) and to a smaller extent the vitreous body (VB) Corneal curvature radius (CR) and axial lengths (AL) are almost unchanged CT = corneal thickness

Results

Variation of ocular dimensions with age and sex in adults

The relationship between *ocular dimensions and age* in each sex is shown in Table II based on linear regression analyses The calculated mean values at arbitrary ages 20 and 70 years are included Fig 1 illustrates the changes observed over this 50 years span of adult life While CD CR and AL parameters showed almost no age variation highly significant changes were found in the anterior segment decrease of ACD_u and increase of LT (both sexes) and decrease of CT (significant in men only) This age reduction of CT was an unexpected finding which will be analysed separately in a following paper

Table III shows the significant advance of the lens with age using two parameters introduced by Lowe (1969) *mid lens depth MLD* with back of cornea as reference and *relative lens position* i e MLD taken as a fraction of total axial length AL A significant reduction of VB was also observed indicated mainly by the significant retrogression of the posterior lens echo However the

Table III

Anterior lens displacement with increasing age

	No. and sex of persons examined	Age (x) $\bar{x}$	Ocular dimension (y) mean $\bar{y}$	standard deviation s_y	regression coefficient b_y	standard error s_b	mean at age 20	mean at age [illegible]0
Mid lens position (mm) = ACD_a CT ½LT = MLD	[illegible]9 M 319 F	4[illegible]8 44.6	4.9[illegible] 4.[illegible]5	0.27 0.30	0.0038 −0.006[illegible] * •	0.0010 0.0010	5.01 4.89	4.8[illegible] 4.[illegible]6
Relative lens position = MLD/AL	[illegible]9 M 319 F	45.8 44.6	0.[illegible]07 0.[illegible]06	0.010 0.010	−0.0001[illegible] • −0.000[illegible] •	0.00003 0.00004	0.212 0.211	0.205 0.200

Sex difference between means MLD $P < 0.001$ MLD/AL $P < 0.05$ • $P < 0.001$

Table IV

Lens position in supine versus sitting position estimated by ultrasonic (u) and optical (o) anterior chamber depth (ACD) measurements

Measurement	No and sex of persons examined	Age (x) $\bar{x}$	Ocular dimension (y) in mm					
			mean $\bar{y}$	standard deviation $s_{y \cdot x}$	regression coefficient b_{yx}	standard error s_b	mean difference at age 30	70
ACD_u	276 M	45.6	3.25	0.33	−0.0160***	0.0012		
$ACD_o + CT$	276 M	45.6	3.11	0.29	−0.0154***	0.0011		
$ACD_u - (ACD_o + CT)$	276 M	45.6	+0.14	0.10	−0.0006	0.0004	+0.15	+0.12
ACD_u	312 F	44.6	3.07	0.35	−0.0173***	0.0013		
$ACD_o + CT$	312 F	44.6	2.97	0.37	−0.0157***	0.0011		
$ACD_u - (ACD_o + CT)$	312 F	44.6	+0.10	0.13	−0.0015 *	0.0004	+0.13	+0.06

$ACD_u - (ACD_o + CT)$ differed from zero in both sexes ($P < 0.001$) and was higher in men than in women ($P < 0.001$)
Correlation coefficients of ACD_u and $ACD_o + CT$: $r_M = 0.97$ and $r_F = 0.96$
** $P < 0.01$ *** $P < 0.001$

conspicuous growth of the lens seems to reduce ACD_a much more (e g in men 0.51 mm/50 years) than VB (e g in men 0.34 mm/50 years) i e *the lens moves forward* (e g in men 0 19 mm (MI D) + 0 03 mm (CT) = 0 22 mm/50 years in women 0.33 mm 50 years)

Lens position body position and age In Table IV the effect upon ACD of sitting versus supine position is analysed through the difference between optical and ultrasonic measurements of the same 358 persons *Two results were obtained Firstly a 0 10 to 0 14* mm deeper chamber was found in the ultrasound survey This measurement took place two years after the optical one i e a shallowing of about 0 03 mm should have been expected On this basis a lens retrogression in the supine position was strongly suggested However systematic discrepancies may exist between the ultrasonic and optical methods Furthermore a comparative ultrasound study revealed higher ACD_a values with my Ekoline 12 technique than with two other (Kretz) equipments (Hedelius & Alsbirk 1975) The second result was less sensitive to technical problems The supine minus sitting ACD difference was found to be slightly *smaller* with increasing age significantly so in women Consequently my working hypothesis *increasing looseness of the heavier lens with age* received *no support* with respect to mobility in a *backward* direction

The conspicuous *sex difference* in ocular dimensions appeared in all parameters except LT The regression coefficients showed no sex difference apart from that of CT The reduction of CT with age was significantly more pronounced in males AL was found to be slightly smaller with increasing age in women not in men Probably this finding bears some relation to the trend towards hypermetropia in elderly females cf RI in Table II

Heritability of ocular dimensions and refraction

In the community examined a fairly large number of complete families was represented Oculometric family studies have been published with respect to ACD and CD In both parameters a major genetic determination was indicated (Alsbirk 1975b c d) As to the ultrasound and refraction surveys the somewhat smaller number of families available were examined in a corresponding way cf Table V CR and AL showed a family resemblance very close to that of ACD for which the analysis was repeated for purposes of comparison Following the age and sex correction applied (cf Alsbirk 1975b) the residual variation of ACD must be due to variations of the basic lens position with respect of top of corneal dome No marital resemblance was found and consequently assortative mating and the influence of major familial environmental factors on ocular anatomy were improbable *In conclusion* the familial correlations of *corneoscleral size* (CR CD AL) as well as *lens position* within the eye ball (ACD DS) indicated a fairly high degree of familial re

Table V

Family correlations in 1st degree relatives and marital pairs ACD DS values are based on age and sex corrected ACD deviation scores cf Alsbirk (1975b)

Relatives	No of pairs	Correlation coefficients				Maximal genetic expectation
		CR	AI	ACD DS	RF	
Father – son	23	0.34	0.55	0.50	0.24	0.5
Father – daughter	29	0.32	0.27	0.30	0.09	0.5
Father – child	52	0.33*	0.41**	0.47***	0.12	0.5
Mother – son	51	0.43	0.29	0.34	0.2[illegible]	0.5
Mother – daughter	56	0.30	0.28	0.1[illegible]	–0.07	0.5
Mother – child	107	0.39***	0.28**	0.24*	0.03	0.5
Parent – child	1[illegible]9	0.3[illegible]**	0.30	0.37***	0.09	0.5
Midparent – child	49	0.43*	0.39*	0.51***	0.03	0.71
Husband – wife	103	0.02	0.04	0.00	–0.09	0.0

Significance against zero in pooled groups * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

semblance. A heritability (h^2) of 0.6–0.8 (≈ 2 x child parent correlations) was found, i.e. *60–80 % of the variations in these parameters seem to be genetically determined.*

As to RI, the study indicated a much lower level of resemblance which did not differ significantly from zero, although positive correlations were mostly obtained. However, it must be admitted that the RI distributions differed from a Gaussian shape by leptokurtosis and myopic skewness in this as in all other studies, and therefore the correlation procedure is to some extent invalidated.

Discussion

Throughout life a well coordinated dimensional anatomy of the eye is the prerequisite of a well focused retinal image. The present results contribute to our general understanding of the age influence in adults and seem further to stress that ocular anatomy has a genetic basis.

The present material was collected stepwise through a three year period and was thus less complete than the initial ACD survey (Alsbirk 1974a). However, the loss did not severely reduce the material which is among the larger ones in oculometric literature. Although the study was carried out under fairly primitive conditions, the precision of the measurements was found to be satisfactory for the purpose.

In their comprehensive survey on clinical oculometry Delmarcelle et al. (1976) have recently reviewed our knowledge within this field. The present analyses show that the *size of the corneoscleral envelope remains almost constant throughout adult life*: AL, CD and CR showed almost no age variation judged by the present population study. However, no general agreement concerning this simple and plausible finding seems to exist. Although CR (and CP) show stationary values in most studies, some authors state that AL is smaller in old persons, e.g. Gernet & Franceschetti (1967) and François & Goes (1969). Leighton & Tomlinson (1972) likewise found a smaller AL in older emmetropes than in younger emmetropes, and also a smaller CD. They asserted that the eyeball becomes smaller with increasing age and related this to the a.c.g. predisposition in elderly persons. The present results do not support these studies. Based on a proper population study in an a.c.g. high risk population the results seem to stress that corneoscleral *age* variation is small and unimportant also as a factor in a.c.g. development (cf. below). It should also be mentioned that Pérez Llorca Rodrigo's data (1971) from a large Spanish sample showed no AL reduction with age. Generally, however, population studies of unselected groups are extremely few. Furthermore, it must be emphasized that all cross

sectional studies may be misleading. Actually age variation ought to be investigated through longitudinal surveys.

The refractive error showed a small trend towards hypermetropia with increasing age as expected according to the subjective procedure used, but in women only, not in men. This material will be described in detail later but no significant excess of myopes was found in adolescents from Umanaq. Young & Leary (1972) examined 71 Eskimo marital pairs with 258 children from Alaska and found a significant change in mean refraction (in cycloplegia) *and* in AL in children towards longer and more myopic eyes.

The Eskimo a.c.g. patients showed shallow chambers largely due to anteriorly sited lenses of a slightly greater thickness compared with Eskimoan controls (Alsbirk 1976). On this background the variations of lens position and thickness with age was looked for with special interest. The results confirmed all earlier findings with respect to *LT increase with age*. More important was the very clear demonstration of an *anterior lens displacement with age*, cf. Table III. This result convincingly supports the less significant findings made by Lowe (1970). Weekers et al. (1973) and Leighton & Tomlinson (1972) were not able to demonstrate this lens movement with increasing age.

The *supine/sitting comparison* showed a *small shift backwards of the lens* but *no* tendency to *increasing* supine lens retrogression with age. Probably the vitreous body cushion and the suspensory ligament are still able to keep even the thick and heavy lens in place in the supine position. Storey & Phillips (1971) demonstrated a significant change of lens position with gravity (0.10 mm) between supine and prone positions in 10 young adults. Jansson (1963) compared ACD measured optically and by ultrasound and found a significant difference (in men) of opposite sign compared with my findings (0.034 mm higher ACD in sitting position, optically measured). Thus the problem of lens mobility has to be further investigated. It seems to be of some importance in elderly persons not less in relation to a.c.g. and to prone position provocative test, cf. Neumann & Hyams (1973).

The *sex difference* of most ocular dimensions (in Table II–III) agrees with all larger studies. The CT sex difference, however, was a new finding which will be discussed elsewhere on the basis of a larger sample including children.

Ethnic differences between Eskimos and Caucasians were analysed recently (Alsbirk 1976) and were only found in the lens position parameters ACD and MLD, and in corneal size (CD), cf. Alsbirk (1975c).

The *family study* presented here gauged the family resemblance of three ocular dimensions and RF within the same material. Nearly identical child-parent correlations were observed with respect to corneal curvature radius (CR), axial length (AL) and the age and sex corrected chamber depth (ACD DS), which is an expression of the basic lens position. It must be emphasized that

these three parameters are interrelated being part of the general eyeball size In the present material the following cross correlations were observed (in 375 persons in whom both eyes were measured) AL CR +0.50 AL ACD DS +0.53 CR ACD DS +0.01 A corresponding CD family correlation was achieved child midparent $r = 0.56$ $h^2 = 0.[illegible]9$ but again highly significant cross correlations were found CD CR 0.44 CD ACD DS +0.49 CD AL +0.42 Thus all studies together indicated that *corneoscleral size and lens position within the eye are to nearly the same extent genetically determined* More than half of the variation (60–80 %) seems to be due to additive genetic factors i e to polygenes

The *refractive error* showed a much smaller family resemblance which did not differ significantly from zero All analyses of this clinically important parameter are complicated by its remarkably leptokurtotic distribution while the ocular dimensions show a Gaussian like pattern also in the present study Considering the total refraction of the human eye about 60 diopters most refractive errors are remarkably small The conspicuous changes in lens thickness and position throughout life occur without major changes in refractive error The stability of RE in adults and its leptokurtosis seem to indicate that active physiologic mechanisms continuously modify the power of the growing lens and succeed in keeping the eye nearly emmetropic also throughout adult life Thus the family resemblance with respect to refractive error is probably weakened in spite of the anatomical similarity between relatives A changing environment may influence this emmetropization in different ways and lead to ametropia as among other findings the Alaskan and Canadian epidemic of myopia suggests Besides Young & Leary (19[illegible]2) found a significant child parent RE correlation ($r = 0.23$) identical with the value found by Sorsby et al (1966) My finding ($r = 0.09$) is somewhat lower probably due in part to the subjective refraction procedure used

In conclusion the age and sex variations of ocular anatomy showed a conspicuous age influence upon lens thickness and position but nearly no age influence upon size of corneoscleral envelope with a generally smaller eye in women Family studies indicated a mainly genetic determination of the ocular dimensions and a mainly non genetic determination of (subjective) refractive error

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References

Alsbirk P H (1973) Angle closure glaucoma surveys in Greenland Eskimos A preliminary report *Canad J Ophthal* 8 260–264

Alsbirk P H (1974a) Anterior chamber depth in Greenland Eskimos I A population study of variation with age and sex *Acta ophthal (Kbh)* 52 551–564

Alsbirk P H (1974b) Anterior chamber depth in Greenland Eskimos II Geographical and ethnic variation *Acta ophthal (Kbh)* 52 565–580

Alsbirk P H (1974c) Optical pachymetry of the anterior chamber A methodological study of errors of measurement using Haag Streit 900 instruments *Acta ophthal (Kbh)* 52 747–758

Alsbirk P H (1975a) Anterior chamber depth and primary angle closure glaucoma I An epidemiologic study in Greenland Eskimos *Acta ophthal (Kbh)* 53 89–104

Alsbirk P H (1975b) Anterior chamber depth and primary angle closure glaucoma II A genetic study *Acta ophthal (Kbh)* 53 436–449

Alsbirk P H (1975c) Corneal diameter in Greenland Eskimos Anthropometric and genetic studies with special reference to primary angle closure glaucoma *Acta ophthal (Kbh)* 53 635–646

Alsbirk P H (1975d) Anterior chamber of the eye A genetic and anthropological study in Greenland Eskimos *Human Heredity* 25 418–427

Alsbirk P H (1976) Primary angle closure glaucoma Oculometry epidemiology and genetics in a high risk population *Acta ophthal (Kbh)* 54 *Suppl* 127 1–31

Alsbirk P H & Forsius H (1973) Anterior chamber depth in Eskimos from Greenland Canada (Igloolik) and Alaska (Wainwright) A preliminary report *Canad J Ophthal* 8 265–269

Clemmesen V & Alsbirk P H (1969) Le glaucome primaire au Groenland *Bull Soc franç Ophtal* 82 243–249

Clemmesen V & Alsbirk P H (1971a) Primary angle closure glaucoma (a c g) in Greenland *Acta ophthal (Kbh)* 49 47–58

Drance S M (1973) Angle closure glaucoma among Canadian Eskimos *Canad J Ophthal* 8 252–254

Drance S M Morgan R W, Bryett J & Fairclough M (1973) Anterior chamber depth and gonioscopic findings among the Eskimos and Indians in the Canadian Arctic *Canad J Ophthal* 8 255–259

Delmarcelle Y François J Goes F Collignon Brach J Luyckx Bacus J & Verbraeken H (1976) Biométrie oculaire clinique (Oculométrie) *Bull Soc belge Ophtal* 172 1–608

Fledelius H (1976) Prematurity and the eye *Acta ophthal (Kbh)* 54 *Suppl* 128 pp 35–46

Fledelius H & Alsbirk P H (19 5) Comparative ultrasound oculometry *Bibl ophthal (Basel)* 83 pp 263–268

François J & Goes F (1969) Comparative study of ultrasonic biometry of emmetropes and myopes with special regard to the heredity of myopia In Gitter Keeney Sarin and Meyer Eds *Ophthalmic ultrasound* pp 165–180 Mosby St Louis

Gernet H & Franceschetti A (1967) Ultrasound biometry of the eye (review) In Oksala and Gernet Eds *Ultrasonics in ophthalmology* pp 1 5–206 Karger Basel New York

Janston F (1963) Measurement of the intraocular distances by ultrasound and comparison between optical and ultrasonic determinations of the depth of the anterior chamber *Acta ophthal (Kbh) 41* 25–61

Leighton D A & Tomlinson A (1972) Changes in axial length and other dimensions of the eyeball with increasing age *Acta ophthal (Kbh) 50* 815–826

Lowe R F (1966) New instruments for measuring anterior chamber depth and corneal thickness *Amer J Ophthal 62* 7–11

Lowe R F (1969) Causes of shallow chamber in primary angle closure glaucoma. Ultrasonic biometry of normal and angle closure glaucoma eyes *Amer J Ophthal 67* 5 91

Lowe R F (1970a) Anterior lens displacement with age *Brit J Ophthal 54* 117–121

Morgan K W & Munro M (1973) Refractive problems in northern natives *Canad J Ophthal 8* 226 228

Morgan R W, Speakman J S & Grimshaw S E (1975) Inuit myopia An environmentally induced epidemic? *Canad med Ass J 112* 575–577

Neuman E & Hyams S W (1973) Gonioscopy and anterior chamber depth in the prone position provocative test for angle closure glaucoma *Ophthalmologica (Basel) 167* 9 14

Pérez Lorca Rodrigo J (1971) Biométrie échographique statistique du segment antérieur et axe antéro postérieur de l'œil humain vivant du nouveau né prématuré au vieillard chez les habitants de Cadix *Bull Soc franç Ophtal 84* 275–280

Skeller E (1954) Anthropological and ophthalmological studies on the Angmagssalik Eskimos *Meddelelser om Grønland 107 (4)* 1–211

Sorsby A Leary G A & Fraser G R (1966) Family studies on ocular refraction and its components *J med Genet 3* 269 273

Storey J K & Phillips C I (1973) Ultrasonic investigations on mobility of crystalline lens In Massin and Poujol Eds *Diagnostica ultrasonica in ophthalmologia* pp 261–264 Centre Nat Ophtal Quinze Vingts Paris

Weekers R Delmarcelle Y Luyckx Bacus J & Collignon J (1973) Morphological changes of the lens with age and cataract In *The human lens – in relation to cataract* pp 25–43 Elsevier Amsterdam

Wessely K (1911) Zur Methodik der Grossenbestimmung des menschlichen Auges nebst Beschreibung eines Instruments zur Messung der Hornhautbreite (Keratometer) *Arch Augenheilk 69* 265–271

Young F A Leary G A Baldwin W R West D C Box R A Harris E & Johnson C (1969) The transmission of refractive errors within Eskimo families *Amer J Optom 46* 676–685

Young F A & Leary G A (1972) The inheritance of ocular components *Amer J Optom 49* 546–555

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A NEW PIGTAIL VARIANT FOR CANALICULUS SURGERY

BY

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A modification of the Worst pigtail probe has been designed and its function is described

Key words pigtail probe – canaliculus rupture – canaliculus surgery

With traumatic rupture of the lacrimal canaliculus it is important at the time of acute surgery to reconstruct the canaliculus as carefully as possible In most cases a stent is used which is introduced into the canaliculus and is left there until healing is completed The most common types of stents are nylonthreads or polyethylenetubes In many cases there may be technical difficulties in introducing the appropriate stent without causing additional trauma Most of the instruments designed for passing stents do not always function quite satis factorily For that reason we have designed a modified pigtail with a lumen to be used together with a nylonthread from Medical Workshop We have had clinical experience with this instrument since 1975

The instrument is manufactured from a needle used for lumbarpuncture with an outer diameter of 0 9 mm This needle is bent in a slight spiralfashioned semicircle with a diameter of about 10 mm and mounted on a nickelplated brass shaft In this shaft a hole is drilled obliquely from one end so that it emerges about [illegible] cm away The bent needle is soldered in the end hole A stainless suture with an olive of silver solder is used as a mandrin The mandrin can easily be brought into the lumen at the tip and out of the hole on the shaft On the back of the shaft there is a little ring lock which keeps the mandrin tight

With a canaliculus rupture the pigtail is introduced into one of the canali culi via the punctum to the rupture Dilatation of the punctum by usual probing

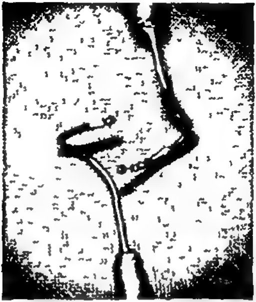

Fig 1
A new pigtail variant for canaliculus surgery

may be necessary so that the olive can be introduced Once the pigtailtip is out in the rupture the mandrin is taken away The nylonthread is passed some cm into the pigtail lumen and the instrument is then drawn back without trauma in the ruptured region or canaliculus The same procedure is then repeated via the other punctum and canaliculus Via the two puncta we now have a continuous stent at the rupture The two ends of the nylonthread are sutured or melted together and bent by means of cautery to prevent them from lying close to the bulb

Up to now we have had the opportunity of using the instrument seven times and it has functioned most satisfactorily

Reference

Worst J G F (19C9) Method for reconstructing torn lacrimal canaliculus *Amer J Ophthal* 53 520– 72

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FLUORESCEIN AND INDOCYANINE GREEN FLUORESCENCE ANGIOGRAPHY IN STUDY OF AFFECTED MALES AND IN FEMALE CARRIERS WITH CHOROIDERMIA

A Preliminary Report

BY

HENRIK FORSIUS LEA HYVÄRINEN HEIKKI NIEMINEN and ROBERT FLOWER

26 males and 13 female carriers of different ages with choroideremia of varying severity were investigated using sodium fluorescein (FAG) and/or indocyanine green (ICG) fluorescence angiography

Females with minor changes present in pigment epithelium may stay unchanged throughout life or gradually develop into a more advanced stage resembling the fundus picture of severely affected males

In moderately affected females there is a patchy degeneration of pigment epithelium in the macula Peripapillary degeneration is seen also in indocyanine green fluorescence angiograms

In males atrophic areas and the remaining choriocapillaris are clearly demonstrated in FAG and less well visible in ICG angiograms ICG angiograms show choroidal vessels more clearly in cases where the pigment epithelium and the choriocapillaris are still present.

In advanced cases in males and females the choroidal blood circulation is slow

Key words choroideremia – blood circulation in eye ground – sodium fluorescein fluorescence angiography – indocyanine green fluorescence angiography – X chromosomal disease

Choroideremia first described in 1872 by Mauthner is a bilateral hereditary progressive degeneration of the choroid and retina characterized by night blindness and visual field constriction in affected males In 1942 Goedbloed & Waardenburg in independent studies stated that choroideremia is carried as an intermediate sex linked (X chromosomal) trate The normal carrier state is characterized by the combination of pigment clumping and depigmentation in the outer retinal layers especially in the midperiphery

No histological studies in carriers have been made but ophthalmoscopically the changes in the slightly affected females are restricted to the pigment epithelial layer of the retina Most authors held the fundus picture to be stationary during the carriers life (McCulloch & McCulloch 1948) but propression has been observed (Kurstjens 1965) Usually the females have no subjective visual symptoms even in old age however some females have been described with an almost homozygotic state in their eyegrounds the opposite is also possible Kurstjens (1965) did not found any changes at all in the fundi of one genetically confirmed conductor

Few reports on pathological investigations have been made and all were on totally blind old males (Grutzner & Vogel 1973 Rafuse & McCulloch 1968) The conjunctival and ciliary vessels were normal as were the retinal vessels, but in those few choroidal vessels which remained thickened and hyalinized vessel walls were seen The Bruch s membrane the pigment epithelium and the outer retinal layers were totally destroyed The cause for the disease is not known The appearance in the carriers and in young males suggests a primary defect in the retinal pigment layer but a primary defect in the choriocapillaris has also been discussed

The fundus picture of an affected male varies with age The earliest changes may be present at birth they have been observed at the age of 1½ years (Kurstjens 1965) These earlier changes were defective pigmentation in the pigment epithelium and pathologically visible choroidal vessels throughout the fundus Atropic changes in the choroid develop during the first decades and result in difficulties with night vision and defects of visual fields Later atrophic areas enlarge and at the age of 40 to 50 years only a small central island of functioning retina is left Defective night vision usually is symptomatic at the age of 5–10 years but some affected males first observe their difficulties in dark adaptation at about 20 years of age In three boys aged 7 9 and 11 years respectively normal adaptation curves were found in the investigation of Kurstjens (1965) all 25 other patients had abnormal night vision curves

Fluorescein angiography (FAG) shows narrow retinal vessels and intense fluorescence in areas where choriocapillaris is visible but no fluorescence where choroidal vessels are absent (Krill et al 1968 Takki 1974) In addition angio

graphy during the late stages demonstrates a slowing of the choroidal and retinal circulations (Gass 1970)

This paper [illegible] a preliminary report of a follow up study of patients with choroideremia The purpose of the investigation is to document changes in both affected males and in female carriers during several years in hope to find some clues to the pathogenesis of this disease

Material and Methods

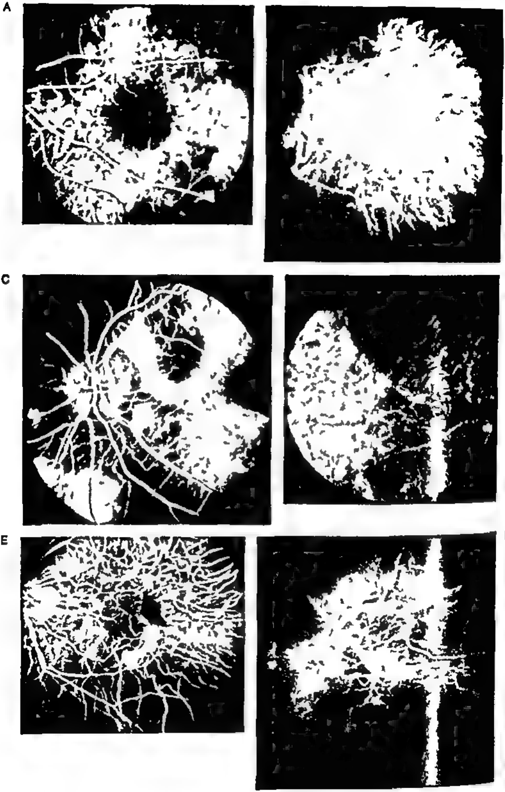
In northern Finland several families with choroideremia have been found The families live far away from each other and no genealogical connection between them has been proved in spite of the fact that the sparse population found in this area (660 000) suggests that the same defect gene is responsible for all those diseased Our largest pedigree consists of 36 affected men and 69 female carriers In an earlier study (Forsius & Eriksson 1976) part of this largest pedigree was showed and the connection of choroideremia with probably autosomal dominant uveal coloboma with low penetrance was discussed

At the end of year 1976 26 males and 13 females of different ages with choroideremia of varying severity were investigated at the Department of Ophthalmology University of Oulu A clinical examination visual fields dark adaptation fluorescein angiography and/or indocyanine green fluorescence angiography was performed (Table I)

Table I

Sodium fluorescein fluorescence angiography (FAG) and indocyanine green fluorescence angiography (ICG) Distribution of the material

	Investigated males			Investigated females					
				Slight changes			Severe disturbancies		
	Age < 25	> 25	Total	I	II	III	IV	V	Total
FAG only	1	2	3	–	1	–	1	–	2
ICG only	–	–	–	1	–	–	–	1	[illegible]
FAG + ICG	10	13	23	1	1	4	[illegible]	1	9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Fluorescein angiography was performed using a standard Zeiss fundus camera modified for fluorescein angiography (Hyvarinen et al 1969) and for indocyanine green fluorescence angiography (Flower & Hochheimer 1976) Angiograms were made at 0 8 second intervals In indocyanine green (ICG) fluorescence angiography the excitation filter transmits energy from about 7500 to 8000 Å and the barrier filter transmits above 8000 Å with peak transmission at 8350 Å corresponding to peak fluorescence of ICG in blood In the lightly pigmented north European eyes the infrared light passes easily through the retinal pigment epithelium and since the indocyanine green dye does not difuse through the vessel walls as does sodium fluorescein blood circulation through choroidal vessels except choriocapillaris can be visualized

Results

Female carriers

The degree of involvement in different female carriers varies greatly Altogether five different stages of choroidal changes can be defined

In cases belonging to the first category (stage I) no changes or changes only in the pigment layer of the midperipheral fundus are seen Those with minor changes present in the pigment epithelium may stay unchanged throuh out life or gradually develop into a more advanced stage these patients have no subjective symptoms The dispersion of granules in the pigment layer is best seen in fluorescein angiograms

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Fig 1 A–F

Fig 1 A Fluorescein angiography (FAG) in a 12 year old boy (H S) Retinal circulation is normal filling of choriocapillaris below the macula above the macula and slightly lateral to fovea is defective The pigment distribution in the pigment layer is granular

Fig 1 B In corresponding indocyanine green angiography (ICG) angiograms the choroidal vessels are clearly demonstrated and the lumen is widely open Smaller vessel branches are not seen well

Fig 1 C 25 year old affected male (M O) with pronounced choroidal degeneration Dark pigmentation in fovea region

Fig 1 D Temporally to the macula choroidal vessels contain fluorescein in the vessel wall in late venous phase

Fig 1 E 6? year old affected male (V I) with only a small residual island of functioning retina in the macula

Fig 1 F Some choroidal vessels (arrows) are visible on a longer pathway in ICG angiogram compared to that in fluorescein angiogram.

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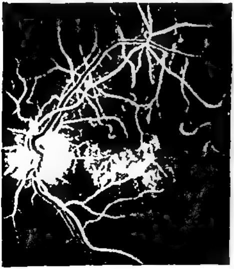

retina were seen Investigation with Goldmann Weekers adaptometer showed only photopic vision Difficulties in night vision in our patients were present before the age of 20 years and changes in dark adaptation could regularly be demonstrated with adaptometer before subjective symptoms appeared The atrophic areas and the remaining choriocapillaris are clearly demonstrated in fluorescein angiograms and less well visible in ICG angiograms (Fig 1 A C)

In severely affected males the choroidal vessel walls seem to be damaged in such a way that they absorbe dye This patchy staining of the vessel wall especially in choroidal veins is visible both in ICG angiograms (Fig 3 D) and in fluorescein angiograms (Figs 1 D 3 F)

In cases where the pigment layer and the choriocapillaris are still present ICG angiograms show choroidal vessels more clearly than fluorescein angio grams (Figs 1 B 2 B) In the most advanced cases only a few choroidal vessels are seen in ICG angiograms and these cases are better studied in fluorescein angiograms

In female carriers except those most advanced and in young boys the filling of retinal and choroidal arteries starts almost simultaneously The difference compaired with normal individuals is very slight Normally the dye is visible

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Fig 3 A–F

Fig 3 A 44 year old female carrier (K K.) with far advanced choroidal changes (stage V) same fundus as in picture (Fig 4 F) ICG angiogram at the moment the dye appears in two choroidal vessels and one retinal artery the dye is already seen through the sclera The remnants of choroidal pigmentation are visible as shadows against the light background.

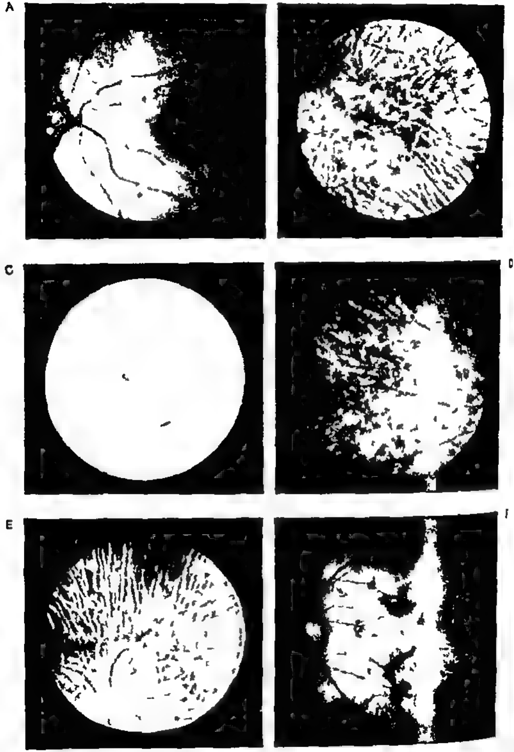
Fig 3 B Very poor filling of choroidal vessels and almost no filling of choriocapillaris Note the attenuated retinal vessels During last few years the patient has had difficulties in night vision and her dark adaptation curve is two log units above normal Normal visual acuity but advanced visual field changes

Fig 3 C 36 year old affected male (H V) Fluorescein angiogram shows changes in peripheral choroidal arteries (early phase)

Fig 3 D He has normal configuration of the choroidal veins at the venous ampulla but some of the veins retain some ICG in their vessel wall (arrow) There is no choriocapillaris present in this area

Fig 3 E 46 year old affected male (P L.) demonstrates clearly the delayed filling of choroid which starts first in early venous phase of retinal circulation. Note the cilio retinal artery at the temporal edge of the disc filling at this time.

Fig 3 F Some choroidal veins retain fluorescein in their wall in late angiogram (arrow) There is only a small central island of functioning retina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in the choroidal vessels slightly before it appears in the central retinal artery In the most advanced female carriers and in all moderately or severely affected males the filling of retinal vessels starts before choroidal vessels and there is a definite delay in filling of choroidal arteries This difference in filling is well demonstrated in a 46 year old affected male who has a cilioretinal artery which fills first in the early retinal venous phase (Fig 3 E)

Discussion

At this stage of the study examination of female carriers has shown that fundus changes vary greatly in their severity from one carrier to another and the changes are possibly progressive as there are so many old female carriers in stages IV and V There apparently are some young carriers with no fundus changes however The morphology of the fundus changes seems to be almost identical with changes seen in affected males However the symptoms in carriers rarely develop to the level of severity found in affected males

In affected males the disease progresses so early that if the early stages of the disease in them is to be studied the affected boys should be studied during their first years of life The findings in young boys resemble those in middle aged carrier females The follow up of the changes in carrier females may give us some clues about what occurs in the affected males during their first years of life

Fig 4 A–F

Fig 4 A 19 year old boy (H S) with choroideremia. Peripapillary pigment and vessel free area Pigment epithelium is dark in fovea Same eye as in Fig 1 A B

Fig 4 B 35 year old male (R V) with choroideremia Pigment epithelium is destroyed and choroidal sclerosis seen in many areas

Fig 4 C 62 year old affected male (V I) with choroideremia Only a small residual island of functioning retina in the macula Same eye as in Fig 1 E F

Fig 4 D 17 year old female carrier (L H) of choroideremia Typical clumping of pigment in pigment epithelium In addition some small hyaloid bodies in outer retinal retinal layers Peripapillary degenerat on visible

Fig 4 E 67 year old female carrier (E V) of choroideremia Destruction of pigment epithelium and choroidal atrophy Same eye as in Fig 2 C D E

Fig 4 F 44 year old female carrier (K K) of choroideremia with advanced retinal and choroidal changes Same eye as in Fig 3 A B

Acknowledgment

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References

Flower R W & Hochheimer B F (19 6) Indocyanine green dye fluorescence and infrared absorption choroidal angiography performed simultaneously with fluorescein angiography *The Johns Hopkins Medical Journal 138* 33–4?

Forsius H & Eriksson A W (19 ?) Choroideremia *Proc ? th Congress of European Society of Ophthalmology* Hamburg 5–9 April

Gass J D M (19 0) *Stereoscopic atlas of macular diseases* pp 110–11? Mosby St Louis

Grutzner P & Vogel M H (19 3) Klinischer Verlauf und histologischer Befund bei progressiver tapeto chorioidealer Degeneration (Chorioideremie) *Klin Mbl Augenheilk 16?* 206–21?

Hyvarinen L Maumenee A E George T & Weinstein G W (1969) Fluorescein angiography of the choriocapillaris *Amer J Ophthal 6?* ?55–6?6

Krill A E Newell F W & Chishti M I (19?8) Fluorescein studies in diseases affecting the retinal pigment epithelium *Amer J Ophthal 6?* 4?0–484

Kurstjens J H (1965) Choroideremia and gyrate atrophy of the choroid and retina *Docum ophthal 19* 1

McCulloch C & McCulloch R J P (1948) A hereditary and clinical study of choroideremia *Trans amer Acad Ophthal Otolaryng 5?* 160–190

Rafuse E V & McCulloch C (19?8) Choroideremia A pathological report *Canad J Ophthal 3* 347–35?

Takki K (19?4) Differential diagnosis between the primary total choroidal vascular atrophies *Brit J Ophthal 58* 24–35

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CHOROIDAL ABSORPTION ANGIOGRAPHY WITH PATENT BLUE V

BY

PER NELLEMANN SØRENSEN

The vital dye patent blue V is used as a negative contrast dye in order to obtain information about the vascular filling events of the choroid in relation to the retinal circulation and the papilla employing intravenous injection and serial photography Patent blue is bound to plasma proteins to a limited degree and the angiograms therefore do not only picture the choroidal vessels but also reveal the filling of the choriocapillaris and the transcapillary exchange It is demonstrated by microdensitometry that the patent blue leakage and subsequent reabsorption is rapid and that the choroidal dilution curve almost parallels that of the retinal vessels Our measurements might indicate a diffusion of patent blue from the choroid to the papillary tissue

Key words angiography – blood brain barrier – choroidal circulation – dye dilution technique – optic nerve – retinal circulation – patent blue V

Fluorescein angiography is an important tool in studying the retinal vascular disorders However apart from animal studies using intracarotid injection of high doses of fluorescein there are important limitations to the use of fluorescein in the study of the choroidal vasculature The three main reasons for this are an absorption of the exciting and emitting light by the haemoglobin on the one hand and by the melanin in the pigment epithelium and the choroid on the other hand and finally the masking effect caused by fluorescein dye leakage from the choriocapillaris which fills within seconds of the dye entering

the eye In order to avoid the filter effect caused by melanin and haemoglobin the dye indocyanine green has been introduced (Kogure et al 1970 Flower 1972) because of its absorption maximum in the near infrared region (800 nm) By this technique using infrared film and appropriate interference filters the vessels are seen in negative contrast The fluorescence of indocyanine green has also been exploited in recent years by refined techniques (Flower & Hochheimer 1973) However the clinical value is not fully elucidated (Orth et al 1976 Craandijk & Beek 1976)

One of the advantages of indocyanine green is that it is almost completely bound to plasma albumin so that the dye does not leak from the choriocapillaris as does fluorescein But this is also one of its limitations thus some pictures taken of choroidal vessels with a deep red interference filter might offer just as much information as indocyanine green fluorescence angiography since only the vessels are pictured

We have tried the opposite view by using a dye which is only to a small extent bound to the plasma proteins in order to obtain information about the transcapillary exchange in the choroid

We chose the non toxic vital dye patent blue V (pontacyl brilliant blue) which has a pronounced absorption peak in the deep red region (at 644 nm in whole blood and 640 nm in plasma and water) well outside the region of the strong absorption by haemoglobin and oxyhaemoglobin (Zijlstra & Mook 1962) and almost outside the region of absorption by melanin (Geraets et al 1960 Behrendt & Wilson 1965 Jensen 1969)

On the other hand the absorption peak is well inside the sensitivity of the commonly used black and white panchromatic films Furthermore the red sensitive materials in some diapositive films have their absorption maximum at about 640 nm (Kodak) For obtaining a quantitative impression of the passage of the dye microdensitometry was performed on the fundus pictures

Methods

50–100 mg (2–4 ml) patent blue V (Guerbet) of the sodium salt was injected in an antecubital vein by square injection Angiography was performed with a Zeiss (Oberkochen) fundus camera equipped with a Nikon F 2 camera body and a motordrive The flash intensity was 350 W/sec The intensity was regulated via the charging voltage and varied less than five per cent An interference filter with a 90 per cent transmission at 640 nm and a band half width of 12 nm was placed in front of the light source

Kodachrome 25 was preferred for black and white films because of better

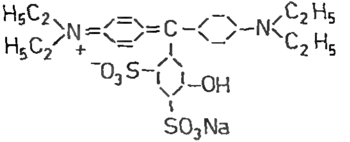

Fig 1
The constitution formula of patent blue V

visual contrast between the red choroid and the black dye The Kodachrome films can only be developed by the manufacturer

The development and a change in the red sensing material was checked by photographing a matt gray disc followed by densitometry of the central area

The microdensitometer consisted of a Reichert microscope combined with a built in photomultiplier with expanded red sensitivity and a built in Schott verlauffilter The density was read at 640 nm on a Grace model 380 densitometer The density was read over the superior temporal vessels at the papillary border over the peripheral and paracentral part of the papilla and over the choroid

Results

At 640 nm the fundus picture is uniform the veins are seen dark and the smaller vessels are invisible The central arterioles are only seen with difficulty The main trunks of the choroidal vessels are seen in blonds and excessive myopes The choroidal pigment pattern is diminished in intensity but still present

When patent blue V is injected iv the total fundus is filled in an even pattern and the area includes the optic disc About one second later the dye appears in the previously invisible arterioles and about two seconds later the venoles becomes darker but no laminar filling can be observed In the course of the next thirty seconds the darkening of the arterioles and venoles fades off but the arterioles can still be seen after 5 min The total fundus fades a little more slowly because of dye leakage into the intervascular spaces and supra choroidal space The choroidal vessels are seen to be almost empty of dye

The dye dilution curves are seen in Fig 2

During the first phase the choroidal dilution curve follows that of the retinal arterioles But later the choroid has a slightly less pronounced decrease

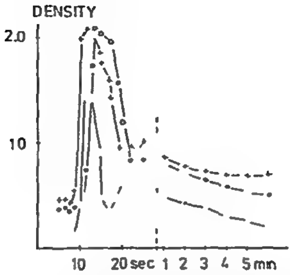

Fig 2

Dye dilution curves of a normal subject recorded from the superior temporal branch arteriole (- -) venole (-o-) and choroid (-+-) one papillary diameter from the papillary edge near these vessels 100 mg patent blue V was injected Density denotes the density of the subtractive colour film read by microdensitometry at 640 nm

which might indicate a leakage of the dye and not a decreased flow The density decrease of the papilla is not as pronounced as the density decrease of the retinal vessels suggesting a diffusion of dye into the tissue of the papilla

Furthermore Table I demonstrates a density increase in the peripheral part of the optic disc in relation to the density of the central part which might indicate a diffusion of patent blue from the choroid

The variation due to change in the characteristics of the films or variation due to the development was small The density of the gray disc was in ten films of different number 0 654 standard deviation of s = 0 015

The variation due to different exposure because of variation in fixation was of less importance In ten successive pictures in a normal subject a density of 0 52 and a standard deviation of s = 0 043 was found by densitometry of the superior temporal vein at the papillary border

Discussion

Patent blue V is rarely used in ophthalmology but the substance is not totally unknown Patent blue V has been used (Beintema et al 1964) to determine the arm to-retina time and its vital staining properties have been exploited

Table I
The increase of peripheral density of the papilla with time in relation to the density of central part of the papilla

	Minutes					
	1	2	3	4	5	6
Peripheral part of the papilla	0 17	0 18	0 20	0 24	0 25	0 28
Central part of the papilla	0 10	0 12	0 11	0 10	0 11	0 12

by Kutchera (1969) to facilitate the finding of retinal tears in retinal detachment and also by Riehm & Podesta (1971) who demonstrated a rapid flow and rapid dye exchange in the albino rabbit choroid by photographing and filming To our knowledge no human dilution curves or angiographic studies have been performed with this dye

Patent blue is obviously not a suitable dye for demonstration of either the retinal or the choroidal vessels with the exception of the late phase in the case of the latter

The advantage of patent blue V is that it gives a quantitative impression of the filling events when monochromatic light is used and under these circumstances the density increase of the film is directly related to the degree of light absorption and also the amount of dye Within the proper exposure range of the film there is a linear relationship between the density of the photographic image and the logarithm of the light intensity reflected from the fundus when the shutter speed is constant Thus a linear relationship exists between the density increase of the photographic image at a given point and the amount of dye according to the Lambert Beer law

Our method is of course not without disturbing inaccuracies

Most evident is the partial influence of the light absorption by the melanin

A quantative estimation of the light absorption is also greatly invalidated by Rayleigh scatter but the degree is unknown However in the deep red region this is of less importance (Vos et al 1964)

A difficult problem is the control of the exposure By proper fixation and photographing we have found that this error can be minimised The problems of the use of different lots of films and variation in the developing are of minor importance

A better and also less time consuming experimental set up is a direct photoelectric measurement (Riva & Ben Sira 1975) but only one or two spots can be measured at the same time by this technique in contrast to our method.

This study demonstrates a very high circulation rate in the choroid and also a rapid reabsorption of dye which has leaked from the choriocapillaris. The findings are in agreement with previous fluorescein angiographic studies (Hyvärinen et al. 1969, Archer et al. 1970).

The earlier appearance of the dye in the choroidal circulation (Archer et al. 1970) than in the retinal artery is confirmed. Moreover the vessels of the optic disc fill with dye before the retinal arterioles indicating that the main vascular supply to the optic disc comes from the choroidal circulation. This is a common fluorescein angiographic finding, but it should be mentioned that the deep red patent blue absorption angiography has a better tissue penetration and that it is related to the amount of dye.

A diffusion of patent blue V into the tissue of the papilla is seen, and this diffusion is faster in the peripheral part of the papilla. This fact can either be taken as a sign of capillary permeability of the choroidal vessels supplying the disc or as a indication of dye diffusion from the choroid (Cohen 1973). Electron microscopical studies (Hogan et al. 1971) show that the capillaries of the optic disc, in contrast to the choriocapillaris, do not have fenestrae in their basement membranes and that the endothelial cells have tight junctions as is the case with the retinal capillaries. This indicates a dye diffusion from the choroid.

The elegant study of Ben Sira & Riva (1975) also points to a dye diffusion from the choroid. They measured the fluorescein accumulation in the optic disc in relation to a non diffusible reference substance, indocyanine green, and they found no evidence of fluorescein leakage from the capillaries of the optic disc.

These preliminary studies with patent blue V suggests that the substance might be a valuable aid in future ocular circulation studies.

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References

Archer D. B., Krill A. E. & Newell F. W. (1970) Fluorescein studies of normal choroidal circulation. *Amer. J. Ophthal.* 69, 543–554.

Behrendt T & Wilson L A (1965) Spectral reflectance photography of the retina *Amer J Ophthal 59* 1079–1083

Beintema D K Mook G A & Worst J G F (1964) Recording of arm to retina circulation time by means of fundus reflectometry A new photo electric method for the diagnosis of internal carotid artery occlusion *Ophthalmologica 148* 163–168

Ben Sira I & Riva C E (1975) Fluorescein diffusion in the human optic disc *Invest Ophthal 14* 205–211

Cohen A I (1973) Is there a potential defect in the blood retinal barrier at the choroidal level of the optic nerve canal? *Invest Ophthal 12* 513–519

Craandijk A & van Beek C A (1976) Indocyanine Green Fluorescence. *Brit J Oph thal 60* 377–385

Flower R W (1972) Infrared absorption angiography of the choroid and some observa tions on the effects of high intraocular pressures *Amer J Ophthal 74* 600–614

Geraets W J Williams R C Chan G Ham W T Guerry D & Schmidt F H (1960) The loss of light energy in the retina and choroid *Arch Ophthal (Chicago) 64* 606–615

Flower R W & Hochheimer B F (1973) A clinical technique and apparatus for simultaneous angiography of the separate retinal and choroidal circulation *Invest Ophthal 1*° 248–261

Hogan M J Alvarado J A & Weddell J E (1971) *Histology of the human eye* Saunders Philadelphia

Hyvarinen L Maumenee A E George T & Weinstein G W (1969) Fluorescein angiography of the choriocapillaris *Amer J Ophthal 67* 653–666

Jensen S (1969) Microspectrophotometric studies of pigment containing cells in the human eye *Acta ophthal (Kbh) 47* 6°5–632

Kogure K David N J Yamanouchi U & Choromokos E (1970) Infrared absorption angiography of the fundus circulation *Arch Ophthal (Chicago) 83* 209–214

Kutchera E (1969) Vitalfarbung der abgehobenen Netzhaut und ihrer Defekte *Albrecht v Graefes Arch klin exp Ophthal 178* 72–87

Riehm E & Podesta H H (1971) *Investigations on the intra and extravascular circu lation in the rabbit choroid with vital staining dyes* Proc int. Symp Fluorescein Angiography Albi 1969 pp 316–317 Karger Basel

Riva C & Ben Sira I (1975) Two point fluorometer for the human ocular fundus *Appl Opt 14* 2691–°693

Orth D H Patz A & Flower R W (1976) Potential applications of indocyanine green choroidal angiography preliminary report *Eye Ear Nose Thr Mon 55* 4–11

Vos J J Munnik A A & Boogaard J (1965) Absolute spectral reflectance of the fundus oculi *J opt Soc Amer 55* 573–574

Zijlstra W G & Mook G A (196°) *Medical reflection photometry* van Gorcum Assen

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From the University Eye Hospital
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PHOTOCOAGULATION IN RETINAL VENOUS OCCLUSION

BY

LEILA LAATIKAINEN

Results of retinal photocoagulation therapy in 26 eyes with retinal branch vein occlusion (RBVO) and in 18 eyes with central retinal vein occlusion (CRVO) are presented. The final visual outcome in eyes with macular oedema (non-ischaemic type of occlusion) did not significantly differ from that reported in various untreated series of branch or central retinal vein occlusion. Neovascular complications in eyes with capillary non-perfusion (ischaemic type of occlusion) could not be prevented with the relatively mild photocoagulation technique (less than 200 xenon burns in CRVO) used in this study. On the basis of this series the value of photocoagulation therapy in improving the visual prognosis in venous occlusion is questionable, and in order to prevent neovascular complications in the ischaemic type of occlusion a more extensive treatment seems to be necessary.

Key words: photocoagulation – central retinal vein occlusion – retinal branch vein occlusion – macular oedema – neovascularisation

During the last few years several reports on photocoagulation therapy in both retinal branch vein occlusion (RBVO) and central retinal vein occlusion (CRVO) have been presented (Krill et al. 1971, Vannas & Raitta 1972, Cairns 1974, Cleasby et al. 1974, Treyler & Nicholls 1974, Wetzig & Thacher 1974, Sedney 1976 and others). The natural course in retinal venous occlusion is, however, very variable. Only recently new information has been obtained from fluorescein angiography about the various retinal responses which greatly determine the prognosis of retinal venous occlusion and therefore partly determine the results of treatment as well.

The three main vascular responses after retinal venous occlusion are (1) venous and capillary dilatation, (2) abnormal vascular permeability and (3) retinal capillary non-perfusion, which can all be easily identified in a fluo-

rescein angiogram Fluorescein angiographic follow up studies on CRVO (Laatikainen & Kohner 1976) and RBVO (Shilling & Kohner 1976) have shown that the extent of retinal capillary non perfusion is the most important factor determining the prognosis of occlusion

Most of the eyes with vessel dilatation and abnormal vascular permeability (non ischaemic type of occlusion) develop macular oedema Macular oedema often resolves spontaneously with full recovery of vision The best visual prognosis is seen in eyes where the leakage is restricted to veins and venules and where the perifoveal capillary arcade is intact (Clemett et al 1973 Laatikainen & Kohner 1976) If the perifoveal capillaries are more seriously damaged with occlusion of some and dilatation and leakage of the others permanent macular changes in the form of chronic cystoid macular oedema or atrophic macula with pigment epithelial changes develop

The natural course in eyes with extensive capillary non perfusion (ischaemic type of occlusion) is entirely different In the ischaemic type of CRVO the visual prognosis is always poor in RBVO the final outcome depends on the size and localisation of the non perfused area The most characteristic late complication in the ischaemic type of venous occlusion is new vessel formation on the optic disc and/or retina or rubeosis iridis

Therefore the rationale of photocoagulation therapy in retinal venous occlusion is (1) to prevent and treat macular oedema (2) to prevent neovascularisation and (3) to treat neovascular complications if already present

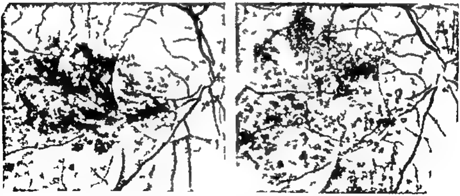

Fig 1

Composite fundus photograph of infero temporal vein occlusion 4 months after initial symptoms (A) Same area 2 months later after photocoagulation showing rapid clearing of oedema and haemorrhages (B) Pre treatment visual acuity of 0 5 has not however improved during 20 months follow up after treatment

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photocoagulation around the macula was used with 200 burns or less so that the most central burns were applied at about 1–2 disc diameters from the fovea The time of treatment varied from 1 to 36 weeks (mean 8 weeks) after the initial symptoms These patients have been followed up for at least one year (22 months on the average) after treatment

Results

At the time of treatment the various types of occlusion (non ischaemic/ischaemic) were not separated but a retrospective study of the pre treatment fluorescein angiograms and retinal photographs showed that 14 of the 26 eyes with RBVO

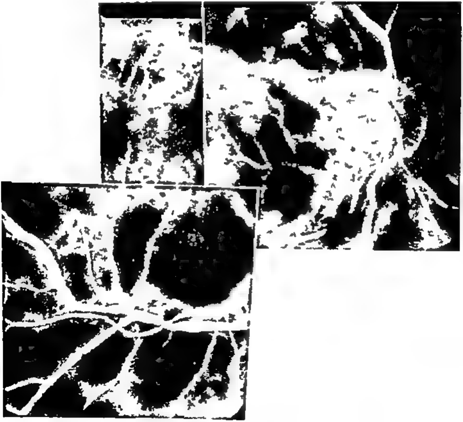

Fig 3
Composite picture of fluorescein angiogram in ischaemic type of CRVO Extensive capillary closure and mild leakage from remaining vessels

Table I

Final condition of 14 eyes with non ischaemic RBVO and of 12 eyes with ischaemic RBVO after retinal photocoagulation

Final condition	Non ischaemic RBVO	Ischaemic RBVO
Full resolution (VA ≧ 0.8)	6	–
Maculopathy	8	6
Disc and or retinal neovascularisation	–	6
Total	14	12

and 11 of the 18 eyes with CRVO had a non ischaemic type of occlusion (Fig. 2 A–B) whereas 12 cases of RBVO and seven cases of CRVO were of the ischaemic type (Fig. 3).

In the group of the non ischaemic type of RBVO six out of 14 eyes recovered completely with final visual acuity of 0.8 or better and eight eyes developed

Table II

Visual prognosis in 14 eyes with non ischaemic RBVO and in 12 eyes with ischaemic RBVO after retinal photocoagulation

Final versus pre treatment visual acuity	Non ischaemic RBVO		Ischaemic RBVO		All cases with RBVO	
	No	%	No	%	No	%
Improved	7	50	4	33	11	42
Unchanged	5	36	5	42	10	39
Deteriorated	2	14	3	25	5	19
Total	14		12		26	

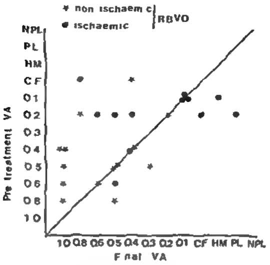

Fig 4

Graph showing final versus pre treatment visual acuity in 26 eyes with RBVO Diagonal straight line = line of no change CF = counting fingers HM = hand movement PL = perception of light NPL = no perception of light

Table III

Final condition of 11 eyes with non ischaemic CRVO and of 7 eyes with ischaemic CRVO after retinal photocoagulation

Final condition	Non ischaemic CRVO	Ischaemic CRVO
Full resolution (VA $\geq$ 0 8)	1	–
Maculopathy	10	–
Disc neovascularisation	–	2
Neovascular glaucoma	–	5
Total	11	7

Table II
Visual prognosis in 11 eyes with non ischaemic CRVO and in 7 eyes with ischaemic CRVO after retinal photocoagulation

Final versus pre treatment visual acuity	Non ischaemic CRVO		Ischaemic CRVO	
	No	%	No	%
Improved	3	2	1	14
Unchanged		64	–	–
Deteriorated	1	9	6	86
Total	11		7	

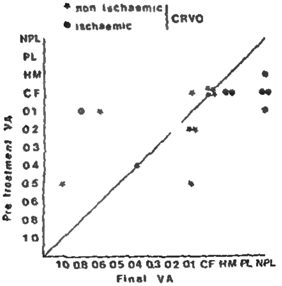

Fig 5
Graph showing final versus pre treatment visual acuity in 18 eyes with CRVO
Abbreviations same as Fig 4

maculopathy either cystoid macular oedema (Fig 1) or atrophy and pigment epithelial changes (Table I) In seven of the 14 eyes the vision improved by at least two lines on the Snellen chart or the final vision was 0 8 or better in five eyes the vision remained unchanged (within one line better or worse) and in two eyes the vision deteriorated (Table II and Fig 4) Seven out of

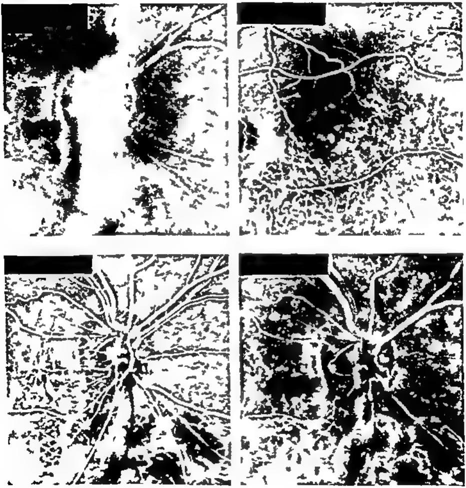

Fig 6

Fluorescein angiogram of ischaemic infero temporal RBVO with disc new vessels 3 years after initial photocoagulation (A) Macula dry with pigment epithelial changes macular capillaries partly occluded (B) After more extensive re treatment disc new vessels regressed (C D)

14 eyes were treated during the first month after the initial symptoms Five of these improved and two remained unchanged

In the group of the non ischaemic type of CRVO only one out of 11 eyes recovered completely the others developed permanent macular changes (Table III) In three eyes the vision improved by at least two lines on the Snellen chart or from counting fingers to 0 1 in seven eyes the vision remained unchanged (within one line better or worse) and in one eye the vision deteriorated (Table IV and Fig 5) No deterioration of visual field or complications related to treatment could be found

The visual prognosis in the ischaemic type of RBVO and particularly in CRVO was worse than in the corresponding groups of non ischaemic cases (Tables II and IV) In two eyes with ischaemic RBVO (Fig 4) and in all but one eye with ischaemic CRVO (Fig 5) the final vision was hand movement (HM) only or worse

Six out of 12 eyes with ischaemic RBVO and two out of seven eyes with ischaemic CRVO developed disc and/or retinal new vessels and five out of seven eyes with CRVO developed rubeosis iridis and neovascular glaucoma (Tables I and III) Fig 6 shows fluorescein angiograms of one of the eyes which developed disc new vessels (Fig 6 A) after ischaemic infero temporal RBVO The initial treatment did not cover the whole non perfused area Because of recurrent vitreous haemorrhages and temporary blurring of vision this eye was re treated three years later After that treatment the new vessels on the disc regressed (Fig 6 C–D) Central visual acuity in this eye has deteriorated from the initial 0 6 to 0 5 at the latest examination due to macular changes (Fig 6 B)

Discussion

Macular oedema due to chronic dilatation and leakage of macular and para macular capillaries is the most common cause of central visual loss in retinal venous occlusion Theoretically the treatment of macular oedema could be directed (1) towards decreasing intraluminar pressure by decreasing arterial inflow in the affected area (2) towards making a barrier and so prevent spreading of the oedema to the fovea or (3) towards occluding the leaking capillaries themselves Photocoagulation therapy may be tried for all these purposes but only localised destruction of the leaking capillaries has had some success In RBVO where the area of capillary damage is relatively small this treatment really may stop the leakage and improve macular oedema but even so the vision does not always improve In the present study the visual prognosis in the group of RBVO as a whole did not significantly differ from that found

earlier by Raitta (1965) at this hospital or what has been reported in some other studies on untreated cases of RBVO (Gutman & Zegarra 1974 Sedney 1976) when the same criteria for visual change are used In this study the prognosis was slightly better in the cases of the non ischaemic type of occlusion treated at an early stage than in the rest of the material although the number of cases was too small to draw any definite conclusions about the significance of the time of treatment

In CRVO with macular oedema the area of capillary damage is more extensive In these eyes the entire area of capillary damage cannot be treated because the central macular area will have to be spared In the present series of the non ischaemic type of CRVO the visual prognosis did not differ from that found by the author in a recent series of untreated cases of CRVO (to be published) Also in the group of CRVO as a whole the final visual outcome corresponded with that presented by Raitta (1965) in untreated cases of CRVO

Neovascularisation on the optic disc and/or retina frequently occurs after RBVO and CRVO although the most disastrous complication after CRVO is rubeosis iridis followed by neovascular glaucoma Recent follow up studies on both diseases have shown that neovascularisation only develops in the presence of considerable retinal capillary non perfusion (Laatikainen & Kohner 1976 Shilling & Kohner 1976) So it seems that the non perfused hypoxic retina would act as a stimulus for neovascularisation It is possible that early photocoagulation of the non perfused retina could serve as a prophylactic therapy of new vessel formation In this study photocoagulation had no effect on the prevention of neovascular complications but the treatment did usually not cover the whole non perfused area Recently some evidence has however been obtained which indicates that a more extensive photocoagulation may be of value in the prevention of both retinal and iris new vessel formation (in preparation) Even after development of new vessels on the disc it seems to be possible in some cases (as also demonstrated in Fig 6) to cause new vessels to regress or at least to prevent progression of neovascularisation (Kohner & Shilling 1976) Similarly rubeosis iridis may decrease or even disappear after pan retinal photocoagulation (Laatikainen 1977)

Conclusion

Abnormal vascular permeability and retinal oedema due to venous occlusion can be reduced by retinal photocoagulation but the value of this treatment in improving the visual prognosis after retinal venous occlusion remains open until controlled randomized studies are available

In the ischaemic type of venous occlusion with extensive capillary non perfusion photocoagulation may be of value in the prevention and treatment of late neovascular complications in the fundus and the iris although vision does not improve But in order to be effective treatment of the whole of the non perfused area in KBVO or pan retinal photocoagulation in CRVO seems to be necessary

References

Cairns J D (19 4) Photocoagulation in the treatment of retinal branch vein occlusion *Austr J Ophthal* 2 5–9

Cleasby C W Hall D I Fung W E & Webster R G Jr (1974) Retinal branch vein occlusion Treatment by photocoagulation *Mod Probl Ophthal (Basel)* 1 254 260

Clemett R S, Kohner E M & Hamilton A M (1973) The visual prognosis in retinal branch vein occlusion *Trans ophthal Soc U K* 93 523 535

Freyler H & Nichorlis St (19 4) Lichtkoagulation bei retinalen Venenthrombosen. *Klin Mbl Augenheilk* 16 50 55

Gutman F A & Zegarra H (19 4) The natural course of temporal retinal branch vein occlusion *Trans amer Acad Ophthal Otolaryng* 78 178–192

Kohner E M & Shilling J S (19 6) Retinal vein occlusion In Rose F C Ed *Medical Ophthalmology* pp 391–427 Chapman & Hall London

Krill A E Archer D & Newell F W (1971) Photocoagulation in complications secondary to branch vein occlusion *Arch Ophthal (Chicago)* 85 48–60

Laatikainen L (19 7) Preliminary report on the effect of retinal panphotocoagulation on rubeosis iridis and neovascular glaucoma *Brit J Ophthal* in press

Laatikainen L & Kohner E M (1976) Fluorescein angiography and its prognostic significance in central retinal vein occlusion *Brit J Ophthal* 60 411–418

Raitta C (196) Der Zentralvenen und Netzhautvenenverschluss Ein klinischer Bericht uber 400 Falle unter besonderer Berucksichtigung des intraokularen Druckes und der spaten Fundusveranderungen *Acta ophthal (Kbh) Suppl* 83

Sedney S C (1976) Photocoagulation in retinal vein occlusion *Docum ophthal (Den Haag)* 40 1–241

Shilling J S & Kohner E M (19 6) New vessel formation in retinal branch vein occlusion *Brit J Ophthal* 60 810–815

Vannas S & Raitta C (1972) Microcirculatory disturbances of occlusive diseases of the eye *Docum ophthal (Den Haag)* 33 345–366

Wetzig P C & Thatcher D B (1974) The treatment of acute and chronic central venous occlusion by light coagulation *Mod Probl Ophthal (Basel)* 12 247–253

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HAEMORRHAGIC MACULOPATHY IN YOUNG ADULTS

BY

TOR FLAGE ANTON BRATBERG SAND and PER SYRDALEN

The results from a retrospective clinical study of a group of patients with a specific macular disease are presented The group includes young adults otherwise healthy with no hereditary diseases The macular disease is as a rule monolateral The lesion consists of a small central nodule surrounded by subretinal haemorrhages retinal oedema and degenerative changes in the adjacent pigment epithelium Fluorescein angiography demonstrates subretinal neovascularization in the central part of the lesion The disease is selflimiting and the lesion develops into a fibrotic scar In some cases small atrophic spots are seen scattered in the eyeground There is no vitreous reaction and no signs of anterior uveitis The clinical picture is identical with the macular lesion reported in the presumed ocular histoplasmosis syndrome

Key words maculopathy in young adults – presumed ocular histoplasmosis syndrome – disciform macular degeneration – fluorescein angiography

In 1939 Rieger described a macular disease which he later called Retinitis exudativa centralis The lesion consisted of a yellowish gray nodule surrounded by retinal oedema and recurrent subretinal haemorrhages The disease was characteristically seen in young adults Later this macular disease has been reported among others by Pau (1968) and François et al (1975)

The purpose of the present article is to draw attention to this macular disease and its characteristics This disease illustrates a special reaction pattern

of the macular area. The same reaction pattern is seen in the presumed ocular histoplasmosis syndrome (POHS) (Miller et al. 1976) and in the senile disciform macular degeneration (Gass 1967).

Material and Methods

Nine patients with ten affected eyes, four males and five females, are included in the material (Table I). The average age at appearance of first symptoms was 27.2 years (17–41). One patient (case No. 6) had bilateral disease. The average follow up period was 50.4 months (11–156). At the time of appearance of first symptoms all the patients were in good health. Case No. 5 had, however, a history of myocarditis and rheumatic fever 13 years prior to eye disease and case No. 8 had a history of hepatitis and renal disease 20 years before the eye disease started.

All patients were examined by the authors. This examination included indirect ophthalmoscopy and slit lamp biomicroscopy with the Goldmann three

Table I

Case No. Sex	Age at appearance of first symptoms	Visual acuity		Follow up period
		Initial exam	Final exam	
1 M	37	5/50	cf 2 m	1 year 10 months
2 F	27	5/ 0	5/20	3 years 8 months
3 F	[illegible]	5/20	5/60	4 years 2 months
4 F	20	cf 2 m	cf 2 m	11 months
5 F	27	cf 0.5 m	cf 4 m	4 years
6 M *	30	5/10	5/10	13 years
	41	5/5	5/5	2 years
7 F	–	[illegible]	5/25	3 years 4 months
8 M	25	5/10	cf 0.5 m	6 years 5 months
9 M	26	5/15	5/40	9 years 8 months

Case No. 6 had bilateral disease, cf. text

mirror lens Colour fundus photographs were taken and fluorescein angiography was performed HLA A B and C typing and histoplasmin skin test were done in all patients except one (case No 2)

Results

In this disease the macular or paramacular lesion develops in three distinctive stages Stage I is characterized by a small subretinal nodule surrounded by slight retinal oedema (Fig 1) The elevation of the sensory retina by the underlying nodule creates small traction folds and retinal striping at the margin of the central oedematous zone Stage II represents the clinically most active

Fig 1

Haemorrhagic maculopathy Stage I Case No [illegible] February 1964 Small subretinal nodule in macular area surrounded by slight retinal oedema Marked striping of the retina at the margin of the central oedematous zone

Fig 2

Haemorrhagic maculopathy Stage II early phase Case No 6 April 1964 Increased size of the lesion Increased retinal striping and small subretinal haemorrhages

Fig 3

Haemorrhagic maculopathy Stage II fully developed Case No 6 June 1974 Extensive sectorial subretinal haemorrhages

Fig 4

Haemorrhagic maculopathy Stage III Case No 6 December 1976 A fibrotic scar surrounded by a zone of pigment epithelium atrophy

phase In this stage the central part of the lesion is seen as a well demarcated dark brown subretinal oval tumour The diameter of this tumour does usually not exceed one disc diameter The tumour is surrounded by retinal oedema 2–3 disc diameters in size Subretinal haemorrhages in the lesion are very characteristic findings at this stage (Fig 2 and Fig 3) Stage III represents the inactive healed lesion In this phase the central brown tumour has developed into an irregularly shaped subretinal fibrotic nodule This fibrotic nodule is surrounded by a fairly large zone of sharply demarcated pigment epithelial atrophy (Fig 4)

The above mentioned account in our opinion represents the typical clinical picture of the disease Occasionally waxy deposits can be seen and in three of our patients a few small atrophic spots were seen dispersed in the eyeground One patient had an atrophic halo surrounding the optic disc

The disease develops over the course of several years Stage I was seen in only one patient (case No 6) In the course of four months the disease in

this patient developed into Stage II Based on the case histories it is assumed that Stage I is of relatively short duration (one to four months) Stage II lasts for a considerably longer time than Stage I often two to three years When Stage III is reached the lesion is stable No case of recurrence has been seen by us

The visual loss in Stage I is not very pronounced This conclusion is drawn because only one patient came to our attention complaining of visual loss with a Stage I lesion As the lesion increases and develops into Stage II the visual loss is clearly noticed by the patient as a central or paracentral scotoma (Table I) Most likely the acute visual reduction noticed by these patients is caused by subretinal bleeding The permanent visual impairment corresponds to the visual loss seen in Stage II Thus the healing of the lesion does not affect the degree of retinal damage

Fluorescein angiography Case No 6 was seen in Stage I but angiography was not performed at that time (1964) In Stage II however the lesions show a characteristic angiographic picture In the arterial phase tufts of small vessels in the central lesion fill with fluorescein These vessels have no connection with the retinal circulation In arterio venous phase these vessels leak fluorescein An example from one of our angiographic series is seen in Fig 5 In the late angio graphic phase fluorescein spreads into the surrounding tissue (Fig 6) This an giographic picture is typical of subpigmentepithelial neovascularization In some cases the filling of fluorescein is synchronous with the choroidal flush but in other cases the filling of the new vessels has been seen to be strikingly delayed This delayed filling can be the result of a partial obliteration of the new vessels and in Stage III the vessels can no longer be demonstrated In this stage the angiographic picture corresponds to an atrophic scar with a central fibrotic area (Fig 7)

All patients were apparently in good health at the time of observation Supplementary examinations including laboratory tests Dye test and chest X ray were all negative Histoplasmin skin test was negative HLA A B and C typing did not reveal any particular antigen frequencies (typing was performed at the Tissue Typing Laboratory National Hospital of Norway and at the Institute of Public Health Oslo Norway)

Treatment Steroid therapy and photocoagulation have been advocated Such treatment has been given to some of our patients but the possible benefit of this treatment has not been evaluated Considering the selflimiting nature of this disease it is our opinion that such treatment is of limited value

Fig 5

Haemorrhagic maculopathy Stage II Fluorescein angiography demonstrates subpigment epithelial neovascularization (Case No 4)

Fig 6

Haemorrhagic maculopathy Stage II Late angiographic registration demonstrates the leakage of fluorescein into the macular lesion (Case No 7)

Fig 7

Haemorrhagic maculopathy Stage III Fluorescein angiography in late venous phase shows the central fibrotic nodule surrounded by a zone of sharply demarcated pigment epithelium atrophy No leakage of fluorescein is seen (Case No 6)

Discussion

The disease reported is primarily a disease of the macular area This area is particularly disposed to hereditary degenerative and inflammatory diseases The clinical picture is identical with the macular lesion reported in the pre sumed ocular histoplasmosis syndrome and also has certain characteristics in common with some stages of senile disciform macular degeneration Neovas cularization of the subpigmentepithelial space followed by subpigmentepi thelial or subretinal bleeding is an important pathogenetic factor in the de velopment of these lesions This represents a typical reaction pattern of the macular area though possibly to different pathological stimuli Based on the clinical picture it is not possible to differentiate between the POHS and the reported disease However the histoplasmin skin test was negative and histoplasmosis is rarely reported from this part of Europe (Ellis & Schlaegel 1973) There is thus in our opinion no evidence to support the conclusion that the disease is of histoplasmotic origin The aetiology of the disease is unknown but the age of the patients and the involvement of one eye suggest an inflammatory aetiology The fact that one of our patients had involvement of both eyes the second eye twelve years after the first eye does not contra dict an inflammatory genesis It is probable that the disease develops secondarily to a focal inflammatory cell infiltration of the choroid as suggested by Gass (1967) An association between uveitis and the histocompatibility antigen HLA 27 has been reported (Brewerton et al 1974) In our patients HLA A B and C typing did not reveal any particular antigen frequencies

References

Brewerton D A Caffrey M Nicholls A Walters D & James D C O (1974) Acute anterior uveitis and HL A 27 *Lancet 1* 464

Ellis F D & Schlaegel T F Jr (1973) The geographic localization of presumed histo plasmic choroiditis *Amer J Ophthal 75* 953–956

François J De Laey J J & Dakir M (1975) Choroidopathie maculaire hemorragique chez les sujets jeunes *Ophthalmologica 170* 477–493

Gass J D M (1967) Pathogenesis of disciform detachment of the neuroepithelium III Senile disciform macular degeneration *Amer J Ophthal 63* 617–645

Gass J D M (196) Pathogenesis of disciform detachment of the neuroepithelium V Disciform macular macular degeneration secondary to focal choroiditis *Amer J Ophthal 63* 661–689

Miller S A Stevens T S & De Venecia G (1976) De novo lesions in presumed ocular histoplasmosis like syndrome *Brit J Ophthal 60* 700– 12

Fig 5

Haemorrhagic maculopathy Stage II Fluorescein angiography demonstrates subpigment epithelial neovascularization (Case No 4)

Fig 6

Haemorrhagic maculopathy Stage II Late angiographic registration demonstrates the leakage of fluorescein into the macular lesion (Case No 7)

Fig 7

Haemorrhagic maculopathy Stage III Fluorescein angiography in late venous phase shows the central fibrotic nodule surrounded by a zone of sharply demarcated pigment epithelium atrophy No leakage of fluorescein is seen (Case No 6)

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ARGON LASER TREATMENT OF EXUDATIVE SENILE MACULOPATHY

BY

ANTON BRATBERG SAND

Fourty nine eyes with exudative senile maculopathy (ESM) have been treated with argon laser photocoagulation Fluorescein angiography studies were done pre and postoperatively The follow up time is 6 to 12 months after end of treatment The results suggest a beneficial effect in selected cases of ESM

Key words exudative senile maculopathy (ESM) – fluorescein angio graphy – argon laser photocoagulation – subretinal neovascularisation – visual acuity – complications

During the last few years several factors have caused an increasing interest in exudative senile maculopathy (ESM) The introduction of fluorescein fundus angiography and argon laser photocoagulation have made it possible to treat this disease

Drusen are a predisposing cause of exudative senile maculopathy (Gifford et al 1940 Gragoudas et al 1976) Hogan et al (1972) and others are suggesting that drusen were formed by accumulation of amorphus material between Bruch s membrane and the pigment epithelium Disturbance of the relationship between the pigment epithelium and the choroid may cause a detachment of the pigment epithelium (Gass 1967) with or without growth of choroidal bloodvessels through Bruch s membrane Transudation of plasma or haemorrhage from these abnormal capillaris may lead to serous or haemorrhagic detachment of the pigment epithelium

Fig 1 a and b

Fig 1 a Right eye Fluorescein angiography showing subpigment epithelial vessels with serous detachment of pigment epithelium involving fovea

Fig 1 b Same eye after focal argon laser photocoagulation. Neovascularization is no more present and the pigment epithelium has flattend Visual acuity improved

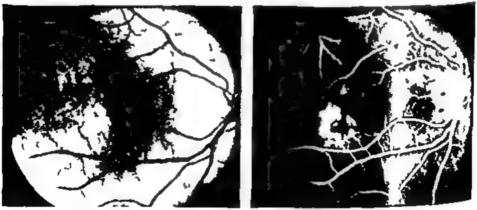

Fig 2 a and b

Fig 2 a Right macula with serous detachment of the pigment epithelium and the sensory retina involving fovea

Fig 2 b Fluorescein angiography of the same macula showing neovascular membrane 1/2 disc diameter from the fovea

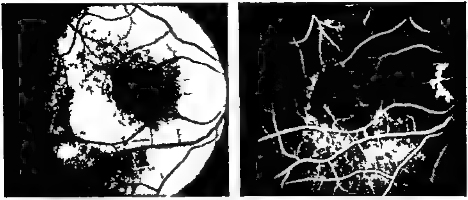

Fig 3 a and b

Fig 3 a Same eye after extensive focal treatment The pigment epithelium and sensory retina are flat Visual acuity improved

Fig 3 b Fluorescein angiography of the same macula showing no subretinal neovascular membrane

The natural history of ESM has not yet been completely defined but progression leads to a disciform scar and redused visual acuity (Gass 1970 Patz et al 1971)

Photocoagulation of ESM has been reported by many authors (Zweng et al 1968 Jebson et al 1969 Gass 1971 Schatz [redacted] al 1973 Bird 1974) The results were disappointing in the early reports but with more experience better results have been obtained In this study 49 eyes with exudative senile maculopathy have been treated by argon laser photocoagulation

Material and Method

During a 3 year period 49 eyes with ESM have been treated by argon laser photocoagulation 33 were women and 16 were men and they ranged in age from 45 to 80 with an average of 64 5 years All the patients were treated in one eye only except for one patient But the second eye of this patient is not included in this study as the follow up period was too short Each patient had a complete eye examination fundus photographs and fluorescein angiography Subretinal neovascularisation was found in 25 eyes (Table I) and haemorrhagic detachment in 6 eyes Fixation photographs were taken to determine the area of fixation An Coherent Radiation argon laser photocoagulator with Zeiss slitlamp delivery system was used on all patients The method of

Fig 1 a and b

Fig 1 a Right eye Fluorescein angiography showing subpigment epithelial vessels with serous detachment of pigment epithelium involving fovea

Fig 1 b Same eye after focal argon laser photocoagulation Neovascularization is no more present and the pigment epithelium has flattend Visual acuity improved

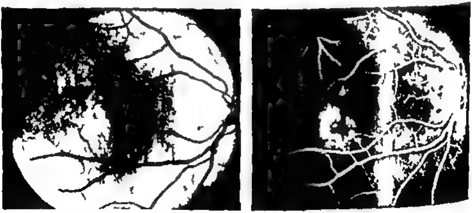

Fig 2 a and b

Fig 2 a Right macula with serous detachment of the pigment epithelium and the sensory retina involving fovea

Fig 2 b Fluorescein angiography of the same macula showing neovascular membrane 1/2 disc diameter from the fovea

treatment used depended upon the location of the pigment epithelial detachment When the detachment was in the fovea or within 1/8 disc diameter (DD) from the fovea a barrage of photocoagulation spots was placed in a horseshoe pattern around the fovea (Figs 5 6 8 9)

A focal and direct way of treatment was used when the point of leakage was more than 1/8 DD away from the fovea (Figs 1 2 3) When neovascularisation was present depending upon its location the same method of treatment as mentioned above was used except that higher energy levels were applied

The patients were instructed to limit their physical activity for about one week and they returned within three to four weeks for examination Fluorescein angiograms were taken 6–8 weeks post treatment and retreatment was done if the pigment epithelial detachment did not flatten A few patients were treated up to four times

Results

Table I shows the result of the study 44 9 % improved 46 3 % remained unchanged and 8 2 % worsened Patients classified as better improved their visual acuity at least 2 lines on the Snellen chart and remained so during the follow up period of 6 to 12 months

Unchanged means that the eyes retained their previous vision within one line of the Snellen chart Worsen did those patients which during the follow up period had a drop of vision of at least 2 lines on the Snellen chart A comparison was made between the preoperative visual acuity and the result of

Table I
Result of argon laser treatment of exudative senile maculopathy

	Better	Unchanged	Worse
No of patients	22	23	4
Per cent	44 9 %	46 9 %	8 2 %
Neovascular (preop)	7	14	4
Haem detachment (preop)	1	3	2
≧ 6/20 (preop)	16	9	0
6/30–6/60 (preop)	2	4	3
Count fing (preop)	4	10	1
Age average	6[illegible]9	64 4	[illegible]

the treatment (Table I) It seems that the eyes with 6/20 or better before treatment have a greater chance of improvement 2 patients with preoperative vision of 6/8.5 were also treated because of disturbing metamorphopsia The pigment epithelial detachment flattened vision improved and metamorphopsia discontinued

Neovascularisation and haemorrhagic detachment (HDPE) preoperatively seems to be unfavorable (Table I) In the improved group the relative incidense of neovascularisation and HDPE were lowest and highest in the worsened group

The age of the patient may be of a prognostic sign The average age of the patients were lowest in the improved and highest in the worsened group (Table I) One patient with unchanged vision had a long standing (possibly 3–4 years) detachment of pigment epithelium and the sensory retina and developed cystoid changes in the macula although the detachment flattened after horseshoe pattern treatment (Fig 8 a + b)

Obvious complications as a consequence of the treatment with argon laser photocoagulation were seen in 2 eyes in the worsened group One patient with subretinal neovascularisation developed a much larger subretinal neovascularisation membrane post treatment (Fig 7 a + b) Fig 9 a + b shows a patient with haemorrhagic detachment who post treatment developed a large subretinal and subsensory haemorrhage

Discussion

Most cases of senile macula degeneration are believed to be caused by sclerosis and obliteration of the choriocapillaris while Hogan (1972) emphasized the ageing changes in the pigment epithelium and Bruch s membrane The leakage of fluid in the exudative senile maculopathy is most likely from the choriocapillaris through Bruch s membrane or through a defect in this membrane *or from neovascularisation that has grown through breaks in Bruch s membrane.* The sensory retina is usually detached over a pigment epithelial detachment

In some cases of ESM spontaneous flattening may occur but visual acuity does not improve because of retinal changes as a result of prolonged detachment

Certain cases of ESM may resolve after photocoagulation treatment (Zweng et al 1968 Jebson et al 1969 Gass 1971 1973 Schatz et al 1973 Bird 1974 L Esperance 1971) and there is little doubt that they have benefitted from the treatment

The visual results seem poorer when neovascularisation and/or haemorrhagic detachment is present and the patients should preferabely be treated before

drop of visual acuity below 6/20 It is also reasonable to believe that younger patients respond better to treatment than older patients

The introduction of argon laser photocoagulation with the slit lamp delivery system makes it possible to treat more accurately and with a heigher degree of safety The techniques of treatment are essential to the success of photo coagulation (Schatz et al 1973 Bird 1974) Focal direct treatment should be used when the lesion is small and 1/8 disc diameter from the fovea Horseshoe pattern photocoagulation is recommended when the lesion is more extensive and involves the fovea

Fluorescein angiography is essential in selection of cases for treatment and angiograms are recommended after 6–8 weeks after photocoagulation

If flattening has not taken place retreatment is indicated

Complications as a consequence of treatment do occur (Gass 1972 François et al 1975 Schatz et al 1973) (Fig 7+9) Thus great care and experience should be emphasized in the treatment of macular lesions At the present time photocoagulation is the only method of treating EMS

One may conclude from the results of this study that photocoagulation is justified in certain cases of exudative senile maculopathy

We still do not know the long time results of this treatment If we however can give some patients a better vision for only a few years we will find photo coagulation indicated

References

Bird A C (1974) Recent advances in the treatment of senile disciform macular dege neration by photocoagulation *Brit J Ophthal 58* 367–3[illegible]

François J et al (1975) Neovascularisation after argon laser photocoagulation of macu lar lesions *Amer J Ophthal 79* 206–210

Gass J D M (1967) Pathogenesis of disciform detachment of the neuroepithelium *Amer J Ophthal* [illegible] 617–644

Gass J D M (19 0) *Steroskopic Atlas of Macular Diseases* C V Mosby Co St Louis

Gass J M D (1971) Photocoagulation of macular lesions *Trans amer Acad Ophthal Otolaryng* [illegible] 580–605

Gass J D M (1972) Options in the treatment of macular diseases *Trans ophthal Soc U K 9* 449

Gass J D M (1973) Drusen and Disciform Macular Detachment and Degeneration *Arch Ophthal 90* 206–217

Gifford S R & Cushman [illegible] (1940) *Arch Ophthal* 23 60

Gragoudas E et al (1976) *Arch Ophthal 94* 755–[illegible]

Hogan M J (1972) *Trans amer Acad Ophthal Otolaryng 76* 64

Hogan M J Alvarado J Weddell J [illegible] (??) *Histology of the Human eye An Atlas and Textbook* p 344 Sanders Philadelph a

Jebson C N & Wetzig P C (1969) Photocoagulation in disciform macular degeneration *Amer J Ophthal 67* 9?0–930

L'Esperance F A (1971) *Trans amer Acad Ophthal Otolaryng 75* 609

Patz A Maumenee A E & Ryan S J (1971) Argon Laser photocoagulation of macular lesions *Trans amer Acad Ophthal Otolaryng 7.* ?1–53

Schatz H & Patz A (1973) Exudative Senile Maculopathy *Arch Ophthal (Chicago)* 90 153–196

Schatz H & Patz A (1973) Exudative Senile Maculopathy *Arch Ophthal 90* 19?–?

Zweng H C Little H L & Peabody [redacted] R (1968) Laser photocoagulation of macular lesions *Trans amer Acad Ophthal Otolaryng 72* 3??–355

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CONTRAST SENSITIVITY IN MACULAR DISEASE

A Preliminary Report

BY

JOHAN SJÖSTRAND and LARS FRISÉN

Psychophysical measurements of contrast thresholds for sinusoidal gratings of variable frequency were made in normal controls and in patients with macular disease. Normal controls showed a ∩ shaped contrast sensitivity function comparable with previous reports. Patients with relatively well conserved visual acuity showed a marked impairment in contrast sensitivity for targets of high and intermediate spatial frequencies while patients with more advanced disease showed a pronounced impairment across a larger spectrum of frequencies. Our findings provide insight into the visual difficulties of daily life of patients with macular disease. The determination of contrast sensitivity seems to be an important and very sensitive tool for the detection of early disturbances.

Key words: maculopathy – visual acuity – contrast sensitivity – spatial frequency

Gratings and other spatially periodic visual stimuli of variable contrast have proved to be powerful tools in the study of the physiology of the visual system. This is true both for central vision and for peripheral vision and applies to man as well as experimental animals (Campbell 1974, Hilz & Cavonius 1974, De Valois & Morgan 1974, Berkley et al. 1975). Remarkably, both psychophysical and evoked response studies have shown that contrast sensitivity is considerably higher for stimuli with a spatial frequency around 3–5 cycles

per degree of angle than for stimuli of higher or lower spatial frequencies (Campbell & Robson 1968, Kelly & Savoie 1973, De Valois & Morgan 1974). The normal contrast sensitivity curve, where contrast sensitivity is plotted against spatial frequency, is therefore a ∩ shaped curve. There is evidence that the human visual system may contain channels selectively tuned to narrow frequency bands (Blakemore & Campbell 1969, Campbell & Maffei 1970, Graham & Nachmias 1971, Sachs et al. 1971, Quick & Reichert 1975, Mecacci &

Table I

Summary of contrast sensitivity impairments in patients with various diseases of the macula

Patient No	Age	Diagnosis	Visual acuity	Frequency ranges of impaired sensitivity		
				< 4	4–16	> 16 cycles/degree
1	41	central serous retinopathy	1.0		++	+
2	41		0.9		++	+
3	26		1.5		++	+
4	78	senile macular degeneration	0.8		+	+
5	78		0.7		++	++
6	64		0.7		++	++
7	23	annular macular dystrophy	0.6	++	+	++
8	[illegible]	diabetic retinopathy	0.7			++
9	19	macular oedema	0.6	(+)	++	++
10	52	macular oedema	0.7	(+)	++	++
11	20	acute multifocal posterior placoid epithelopathy	0.5	+	++	++
		the same following resolution	0.9		+	(+)

\+ moderate impairment
++ marked impairment

Spinelli 1976) Thus there may exist not only high frequency channels and low frequency channels that need a high target contrast to respond but also channels tuned to intermediate frequencies with much lower contrast thresholds It is an intriguing possibility that various channels may be differently affected in different disorders of the visual system Not much is known yet in this regard Besides reports of impairment of contrast sensitivity in refractive errors (Freeman & Thibos 1975 Fiorentini & Maffei 1976) changes in contrast sensitivity have been documented in a few patients with neurological disease (Bodis Wollner 1972 1974 1976)

We present here a preliminary review of our findings on contrast sensitivity impairment in patients with disorders of the macula together with findings from normal controls We used sinusoidal gratings of variable contrast and spatial frequency Our television based display is briefly described

Materials and Methods

Patients Ten normal controls (age 19–61 years) and eleven patients (age 19–78 years) with isolated macular disease of different types partook in this study Relevant clinical data are given in Table I

Apparatus The display system was based on black and white television equipment according to the block diagram in Fig 1 Sinusoidal gratings (patterns of light and dark vertical bars with a horizontally sinusoidal light profile)

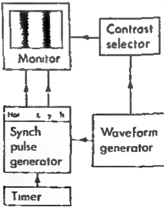
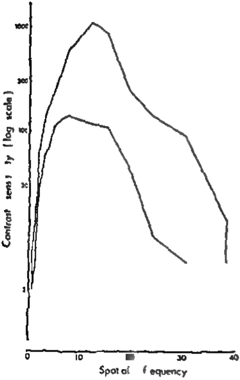


Fig 1

Block diagram of the television based display used for determination of contrast thresholds

were generated electronically on a TV monitor which was masked to subtend 14 x 14 degrees of angle at the eye when viewed at a distance of 5 m The spatial frequency (the number of light/dark cycles on the monitor screen) was varied between 0.4 and 38 cycles/degree The pattern contrast (defined as $(L_{max}-L_{min})/(L_{max}+L_{min})$ where L_{max} and L_{min} denote maximum and minimum luminances respectively) was varied in 2 dB steps in the 0.70-0.0007 range The space average luminance across the television screen was 135 cd/m² it was independent of both spatial frequency and contrast The surround luminance was 20 cd/m²

Procedure The contrast sensitivity curve was determined monocularly by raising contrast from a subthreshold setting at a selected spatial frequency until a grating pattern was faintly seen Sixteen spatial frequencies were



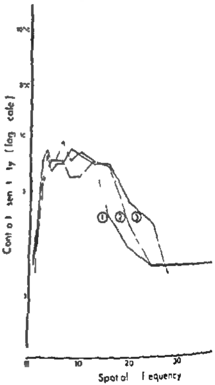


Fig 2
Range of contrast sensitivity at various spatial frequencies in normal subjects

Fig 3
Contrast sensitivity functions of patient Nos 1 2 and 3 (Table I) with central serous retinopathy

explored in random order Contrast sensitivity (the reciprocal of contrast) was always determined twice at each frequency but never consecutively Averaged readings were used as observations Contrast was changed every 2 seconds Refractive errors were carefully corrected for the test distance Miotics mydriatics or artificial pupils were not used

Results

The range in contrast sensitivity for normal subjects is represented in Fig 2 It is likely that the normal range may decrease by correcting for age but this requires further study as well as development of a useful statistical procedure All normal subjects had their peak sensitivity somewhere between 8 and 15 cycles/degree

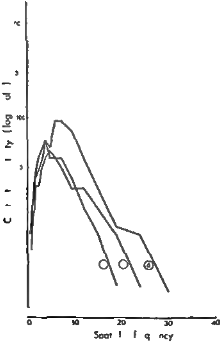


Fig 4

Contrast sensitivity functions of patient Nos 4 5 and 6 (Table 1) with senile macular degeneration

Patients with central serous retinopathy presented contrast sensitivity functions clearly different from those of normal subjects irrespective of very modest reductions in central visual acuity (Fig 3 Table I) The decrease in contrast sensitivity was most marked for high and intermediate frequencies whereas contrast threshold levels were almost unchanged below 2 cycles/degree

A similar change of the contrast sensitivity curve was found in patients with early senile macular degeneration with a visual acuity in the 0 7–0 8 range (Fig 4 Table I) In more advanced cases a marked impairment across the whole spatial frequency range was observed

Contrast sensitivity was similarly affected in patients with other maculopathies (Table I)

Discussion

Irrespective of the small size of our material it is obvious that the usual clinical measure of macular function viz the smallest resolvable optotype of high contrast poorly reflects the visual problems of patients with macular disease Even in patients with minor reductions in visual acuity there was a pronounced reduction in contrast sensitivity across a wide spectrum of spatial frequencies The patient with a macular disorder is obviously handicapped not only in his capacity for resolving fine detail but his contrast threshold is also raised for larger objects In this regard our findings give a sobering insight into the visual problems of the patient with a macular disorder It is important to note that whereas the visual problems of the patient may be partly solved by the use of magnifying optical aids contrast enhancement may be equally important

Our data do not permit the recognition of different types of contrast sensitivity impairment in different macular diseases Likewise our data do not allow conclusions as to the question of differential damage of selectively tuned channels in the visual system This will have to await comprehensive analysis of contrast sensitivity curves from patients with disease elsewhere in the visual system Such studies are presently in progress in our laboratory

Our findings in normal controls differ from those previously reported in that our subjects peak sensitivity occurred at a higher spatial frequency (cf Campbell & Robson 1968 Kelly & Savoie 1973) This is presumably a reflection of the higher space average luminances available in television based display systems as compared to the previously used cathode ray oscilloscopes A neutral density filter put in front of the eye under test resulted in a translation of the sensitivity peak to a lower spatial frequency as obtained in previous studies

employing oscilloscopes (De Valois & Morgan 1974) We consider the higher luminance of a television system preferable in clinical work i e because ordinary acuity tests are made at a similar luminance level Another important factor in the choice of equipment applies to cost and ease of handling We believe that a television based system is superior in this regard

As stated in the introduction the study of contrast sensitivity has proved to be a powerful tool in the study of the normal visual system We believe that this new tool may be equally powerful in the study of the abnormal visual system In particular this approach gives a more sensitive and more penetrating insight into the functional consequences of visual disorders than do currently available clinical tests

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References

Berkley M A Kitterle F & Watkins D W (1975) Grating visibility as a function of orientation and retinal eccentricity *Vision Res 15* 239–244

Blakemore C & Campbell F W (1969) On the existence of neurones in the human visual system selectively sensitive to the orientation and size of retinal images *J Physiol (Lond) 203* 237–260

Bodis Wollner I (1972) Visual acuity and contrast sensitivity in patients with cerebral lesions *Science 178* 769–771

Bodis Wollner I (1974) On dissociated visual functions *Mt Sinai Med 41* 38–45

Bodis Wollner I (1976) Vulnerability of spatial frequency channels in cerebral lesions *Nature (Lond) 261* 309–311

Campbell F W (1974) *The transmission of spatial information through the visual system* The Neurosciences Third Study Program. F O Schmitt and F G Wooden (Eds) The MIT Press Cambridge Mass and London pp 95–103

Campbell F W & Robson J G (1968) Application of Fourier analysis to the visibility of gratings *J Physiol (Lond) 197* 551–556

Campbell F W & Maffei L (1970) Electrophysiological evidence for the existence of orientation and size detectors in the human visual system *J Physiol 207* 635–652

De Valois R L & Morgan H (1974) Psychophysical studies of monkey vision III Spatial luminance contrast sensitivity tests of macaque and human observers *Vision Res 14* 75–81

Fiorentini A & Maffei L (19 6) Spatial contrast sensitivity of myopic subjects *Vision Res 16* 437–438

Freeman R D & Thibos L N (1975) Contrast sensitivity in humans with abnormal visual experience *J Physiol (Lond) 24* 68 –710

Hilz R & Cavonius C R (1974) Functional organizaton of the peripheral retina Sensitivity to periodic stimuli *Vision Res 14* 1333–1337
Kelly D H & Savoie R E (1973) A study of sine wave contrast sensitivity by two psychophysical methods *Perception & Psychophysics 14* 313–318
Mecacci L & Spinelli D (1976) The effects of spatial frequency adaptation on human evoked potentials *Vision Res 16* 477–479
Quick R F & Reichert T A (1975) Spatial frequency selectivity in contrast detection *Vision Res 15* 637–643

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CENTRAL SEROUS RETINOPATHY AND PRESENILE DISCIFORM EXUDATIVE MACULAR DEGENERATION

Is There an Aetiological Relationship Between These Two Exudative Conditions of the Macula?

BY

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and NORMAN NIELSEN

The clinical syndromes central serous retinopathy (RCS) and presenile exudative disciform macular degeneration (PEDMD) are well known but the causes of the pathophysiological and pathoanatomical changes in the choriocapillaris Bru h s membrane and pigment epithelium as predisposing factors are unknown Apparently these two degenerative macular conditions are different However they possibly represent two manifestations of the same nosological entity which is initially dominated by a subretinal exudation in the macular region
It is therefore also reasonable to consider that RCS can be part of or an initial stage of PEDMD In the present study these possibilities have been demonstrated by a follow up examination using among other things fluorescein angiography of a selective material of 90 patients with RCS In addition it is shown that RCS can be a more serious condition with regard to the central vision than is generally accepted

Key words central serous retinopathy (RCS) – presenile exudative disciform macular degeneration (PEDMD) – relationship – prognosis – fluorescein angiography

Fluorescein angiographic studies in later years have given us a greater understanding of the nature of exudative macular disease. This group of diseases includes among others presenile exudative disciform macular degeneration (PEDMD) and central serous retinopathy (RCS). The definition of both RCS and PEDMD is still mainly clinical. The exudative element constitutes the common feature of these two diseases. The most important differences are that PEDMD is often 1) bilateral and 2) has a poor prognosis with regard to the central vision. It has previously been generally accepted that RCS was a benign self limiting disease with spontaneous regression in the course of a few weeks. The object of the present work however is to show that RCS can cause permanent sequelae such as degenerative pigment epithelial changes and macular pigment epithelial detachment. Further that RCS can be a far more serious condition than has previously been presumed. In addition we will point out and discuss the possibility of a relationship between RCS and PEDMD.

RCS was first described by von Graefe in 1866 under the name central recurrent retinitis. The condition has since had many names, for example retinitis centralis angioneurotica (Horniker 1930), juvenil disciform macula degeneration (Verhoeff & Grossman 1937), central angiospastic retinopathy (Gifford & Marquard 1939), serous disciform detachment of the macula (Maumenee 1959) and idiopathic central serous choroidopathy (Gass 1967). These many names illustrate the uncertainty that has been and still is present regarding the aetiology of the disease. Many investigators have attempted to elucidate the aetiology of RCS and among the tentative suggestions the following are worthy of mention: inflammation, infection, toxic or allergic factors, vasomotor phenomena or degenerative changes or possibly multiple factors.

Histopathological studies of eyes suffering from RCS only appear to have been carried out twice. Klien (1953) found serous detachment of the macula, while the pigment epithelium and Bruch's membrane were normal. Later Klien (1961) presumed on revision of the same cases that an increased venous pressure and eosinophilia of the chorioridal vessels were evidence of a type of allergic factor causing serous detachment of the macula. Maumenee (1965) found serous detachment of the neuro epithelium. The chorioidal and retinal vessels were normal. The theory of Gass (1967) that the cause should be sought in the choriocapillaris is still generally accepted to day. This has however not been confirmed histologically.

According to Gass (1967) the predilection for localized detachment of retinal pigment epithelium (RPE) and retina depends on a haemodynamic stress on the posterior choriocapillary bed.

With the choriocapillaris as the starting point diffusion of serous fluid can via Bruch's membrane together with simultaneous loosening of the RPEs

Fig 1

Central serous retinopathy 35 year old man The fluorescein angiogram of the right eye (?17 seconds) shows a serous detachment of the retina The diffusion of fluorescein rises like smoke in an upward direction from the point of leakage

binding to Bruch s membrane and of the binding between the cells of the RPE explain the clinical and fluorescein angiographic picture The reason why this takes place is not known

It is easy to observe detachment of the neuro epithelium by means of oph thalmoscopy or a contact lens As a rule it is not too difficult to see one or more possible detachments of the RPE as light greyish circumscript elevations below the neuro epithelial loosening In general the RPE detachments are smaller than those of the neuro epithelium There can thus be detachment of both the RPE and neuro epithelium while in other cases there is only loosening of the neuro epithelium

In early fluorescein angiograms the site of leakage can be seen as a hyper fluorescent point in one of the macular quadrants most frequent (32 %) super nasally to the macula (Wessing 1972) The classic leakage which is rarely seen can be observed as a mushroom shaped fluorescence (Fig 1) whereas the most frequent type of leakage is circular spreading out in all directions (Fig 2) This type was found by Wessing in 144 of 223 eyes with RCS Kolin & Oosterhuis (1975) found oozing from several points in 15 % of their cases The fluorescein angiogram does not only show a detachment of the neuro-epithelium in cases of RCS but can also demonstrate an eventual simultaneous loosening of the retinal pigment epithelium and the exudations lying below

The term presenile macular degeneration covers an exudative disciform lesion occurring in the macula before or around the age of 60 years. The retinal pigment epithelium is seriously involved in nearly all the diseases of the macula and presenile degeneration is mainly a swelling of the macula (Fig 3) in which the retinal pigment epithelium and the retinal layer are elevated by fluid from the chorioid (Kornzweig 1974). The same picture can be seen with RCS. This serous detachment in presenile degeneration can in a few cases (5 %) be transient or persist unchanged for some considerable time (50 %) while (45 %) progress and become scarred (Chandra et al 1974). A pigment epithelial dystrophy with a reticular pigment pattern can occur in cases of persistent detachment of the pigment epithelium (van Winning & Oosterhuis 1974).

Histological changes particularly in Bruch's membrane such as thickening and hyalinization, granular transformation, intercapillary thickening and fibrillary degeneration are found in presenile macular degeneration (Ho an 1967). A yellowish white hyaline material becomes deposited below the pigment epithelium; this can be seen as the so called "drusen". In addition sub pigment epithelial lipoid accumulations, exudation and new vessel formation can also be seen. Haemorrhage and scarring appear later. Hogan (1967) points out that the physiological ageing begins around 20 years. These changes begin in Bruch's membrane with a gradual accumulation of vesicles in the inner collagenous zone.

Fig 9

Central serous retinopathy 28 year old man. The fluorescein angiogram of the right eye shows *diffusion of fluorescein in all directions from the circular point of leakage*

Fig 3

54 year old man The fluorescein angiogram of the left eye (24 seconds) shows degeneration and irregular mottling of the retinal pigment epithelium with exudation of dye under the pigment epithelium A central serous retinopathy has not previously been seen in this eye similar degenerations are present in the fellow eye

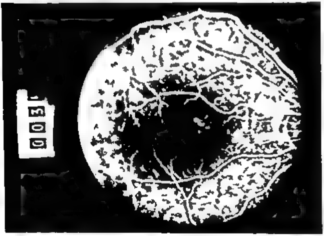

Fig 4

Same patient as Fig 2 A fluorescein angiogram reveals a small atrophy of the retinal pigment epithelium on the nasal side very close to the fovea three years after an untreated central serous retinopathy in the right eye

Material and Methods

The material included 20 patients between the ages of 29 and 48 years average 39.6 years. Six were women and 14 men. The patients were referred to the Eye Clinic by practicing ophthalmologists. The patients were followed up from 2 months to 72 months (average 24 months) after the diagnosis of RCS had initially been made. Both the first and last examination included visual acuity, pressure measurement, visual field, Amsler's chart, slit lamp ophthalmoscopy and at times contact lens, colour photography of the fundus and fluorescein angiography. Five ml of 10 % sodium fluorescein were used for the fluorescein angiography together with film Kodak Tri-x and Topcon camera model TRC F. Eleven of the 20 patients were treated by photo coagulation. The period that passed from the time of diagnosis of the RCS to the commencement of treatment was on average 8 weeks.

Results

One of the 20 patients was both subjectively and objectively free from symptoms at the time of the follow up examination. Of the remainder 2 had a permanent reduction in vision in the affected eye to 6/18 and 2/36. The remaining 14

Fig [illegible]

54 year old man who was treated with photocoagulation for a central serous retinopathy in the right eye 6 years ago. Present examination 18 seconds after injection of fluorescein the angiogram demonstrates a large irregular patchy area with atrophy of the retinal pigment epithelium temporal and close to the fovea.

Fig 6
46 year old woman A central serous retinopathy had been diagnosed in the right eye sixteen months previously Light applications of photocoagulations were applied initially with good result However fluorescein studies (741 seconds) now reveal recurrence of a retinal pigment epithelium detachment affecting the whole macular region Photo coagulation spots are seen in the distal part of he macula

patients had no or only very slight reduction in vision and only slight sub jective complaints in the binocular function for example a change in colour perception in the eye previously affected by RCS However the physical examination revealed positive findings in all 17 patients (plus the two with considerable reduction in vision) in one or several of the parameters visual field Amsler s chart and ophthalmoscopy

It was possible to carry out fluorescein angiography in a total of 17 patients during the follow up examination Only one of these 17 angiograms wa perfectly normal The remainder had in part small circumscript (Fig 4) in part large geographic degenerative changes (Fig 5) in the central pigment epithe lium In 2 cases central serous detachment of the pigment epithelium persisted after 15 and 22 months respectively (Fig 6)

Discussion

The present material is small and without doubt selective since as already mentioned it consists of patients who have been referred to the Ophthalmo logical Department by practicing ophthalmological specialists In the majority

of cases it has therefore consisted of patients where there has either been a considerable reduction in vision or the course of the disease has been somewhat protracted Kolin & Oosterhuis (1975) found 1 case per 22 000 inhabitants and based on this figure there should have been in the same period (6 years) approximately 130 cases in our population There is the possibility that the disease is even more prevalent inasmuch as it is possible that RCS in some cases can be so mild and of such short duration that the patients do not consult an ophthalmologists Cases can occur where the leak is in the periphery of the macula or outside of the macula area in such patients subjective symptoms will be rare even though they will result in dystrophic changes in the pigment epithelium

Two of our patients i e 10 % had a considerable reduction in vision in the affected eye after RCS In 17 patients there were only very slight subjective symptoms but objectively there were small "scotomas" positive Amsler's chart or ophthalmoscopic changes such as pigment displacement in the macula. In other words in 19 of the 20 patients there were to a greater or less extent sequelae after RCS

Similar sequelae were also found by Nørholm (1969) in no less than 8 of 19 patients while Kolin & Oosterhuis (1975) found a slight reduction in vision and scotomas in 10 %. Atrophic foci can also be found in the contralateral eye Koda (1972) thus found foci in the fellow eye in 10 out of 22 patients

Fluorescein angiography is of the greatest importance at the time of the first examination not only in order to obtain an exact diagnosis but also to localize the leakage in the macula

Fluorescein angiography can show during later examinations whether the macula has returned to normal or not or whether as in the present material atrophic areas are still present in the RPE regions Wessing (1972) reports that in the majority of cases of RCS there remain more or less extended atrophic lesions of the retinal pigment epithelium Kolin & Oosterhuis (1975) also found atrophy of RPE and this atrophy was particularly intense in three patients with a reduction in vision It is not possible for us to determine whether these atrophic zones in RPE are of any importance with regard to the long term prognosis of the vision Can a macula where exudation has once been present be more vulnerable or is RCS a possible etiological factor of presenile exudative macular degeneration? The initial exudation with RCS with detachment of RPE and the presenile exudative macular degeneration would suggest that certain aetiological factors can be the same for both diseases (This appears even more obvious when looking at the cases where a central exudative pigment epithelium detachment remains as was seen in two cases in the present material even though druser or cystoid oedema were not present) Wessing (1972) a d

Kolin & Oosterhuis (1975) reported single cases of RCS that ended in central degeneration of senile character The same was possibly the case in two of Norholm s (1969) patients and in two of the patients in the present material Berrocal (1972) questioned 80 ophthalmologists and reported that half of them had seen a minimum of one untreated patient develop macular degeneration years later Bonnet (1974) has four cases in two families where a senile disciform degeneration of the macula occurred in the first generation and a central serous retinopathy in the second generation This leads to the hypothesis of a possible genetic relationship between the two diseases in these cases Gass (1967) clearly refutes any connection between RCS and senile macular degeneration based on inter alia histopathological and prognostic criteria

The histopathological changes with presenile exudative macular degeneration are well documented while only very few microscopic studies of eyes with RCS are available Additional documentation of a possible relationship between RCS and presenile macular degeneration must thus require more histopathological studies and fluorescein angiographic follow up studies of patients with central serous retinopathy

It is generally accepted that the duration of the exudative process in RCS plays an important role with regard to sequelae such as atrophy on the RPE and persisting detachment of RPE The only possible treatment is photocoagulation and with due regard to the possibility of spontaneous remission our criteria for the treatment are as follows

1) a duration of the exudative condition of 3–4 weeks or more or

2) a loss of vision to less than 6/9

The reason why these criteria have not been fulfilled in our material is that we have not seen the patients from the very start of the condition

References

Berrocal J A (1972) *Current worldwide management of central serous choroidopathy Modern problems in ophthalmology Limitations and prospects for retinal surgery* VIII Meeting of the Jules Gonin Club Miami Florida 239–241

Bonnet M (1974) Choriorétinopathie séreuse centrale et dégénérescence sénile de la macula existe t il un lien entre les deux affections? *Ophthalmol Hop Croix Rousse (Lyon)* 90 /11 1–13

Chandra S R et al (1974) Natural history of disciform degeneration of the macula *Amer J Ophthal* 78 579–58

Gass J D M (1967) Pathogenesis of disciform detachment of the neuroepithelium II Idiopathic central serous choroidopathy *Amer J Ophthal* 63 587–615

Gifford S R & Marquardt G (1939) Central angiospastic retinopathy *Arch Ophthal (Chicago)* 21 211–228

Graefe A von (1866) Über zentrale recidivirende Retinitis *Graefes Arch Ophthal* 12 211–215
Hogan M J (1967) Bruch s membrane and disease of the macula Role of elastic tissue and collagen *Trans ophthal Soc U K* 87 113–161
Hornicker E (1929) Über eine form von zentraler Retinitis auf angioneurotischer Grundlage (Retinitis centralis angioneurotica) *Graefes Arch Ophthal* 123 286–360
Klien B A (1953) Macular lesions of vascular origin II Functional vascular conditions leading to damage of the macula lutea *Amer J Ophthal* 36 1–13
Klien B A (1961) Macular and extramacular serous chorioretinopathy *Amer J Ophthal* 51 231–242
Koda N (1972) The fellow eye syndrome in central serous retinopathy (Japan) *Jap J clin Ophthal* 26 1313–1319
Ref Excerpta Medica Ophthal 281 no 213
Kolin & Oosterhuis J A (1975) Retinal pigment epithelium dystrophy in central serous detachment of sensory epithelium *Docum ophthal* 39 1 1–19
Kornzweig A L (1974) Modern concepts of senile macular degeneration *Journal Amer Geriat Soc* XXII 246–253
Maumenee A E (1959) Serous and haemorrhagic disciform detachment of the macula *Trans Pacif Coast Otoophthal* 40 139–160
Norholm I (1969) Central serous retinitis a follow up study *Acta ophthal (Kbh)* 47 890–899
Verhoeff F H & Grossman H P (1937) Pathogenesis of disciform degeneration of the macula *Arch Ophthal (Chicago)* 18 561–585
Wessing A (1972) Changing concept of central serous retinopathy and its treatment *Trans amer Acad Ophthal Otolaryng* 77 275–280
Winning C van & Oosterhuis J (1974) A fluorographic study of reticular patterns in the fundus *Amer J Ophthal* 77 491–498

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DISCIFORM DETACHMENT OF THE MACULA

I Juvenile Haemorrhagic Macular Choroidopathy

BY

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The clinical findings in six patients with juvenile haemorrhagic macular choroidopathy are described There was no evidence of infection with *Histoplasma capsulatum* The history clinical features and course of the disease suggested that at least in some cases intravascular coagulation in the central choriocapillaris may form the choroidopathy inducing the disciform detachment of the macula Oral corticosteroids could not prevent progression of the lesion which had a poor visual outcome In one patient good therapeutic response was achieved with acetylsalicylic acid which may be useful together with lasercoagulation in the early treatment of this syndrome

Key words chorioidea – disseminated intravascular coagulation – juvenile haemorrhagic maculopathy – macula – presumed ocular histoplasmosis

Although histoplasmosis is rare in Europe cases with lesions similar to those seen in presumed ocular histoplasmosis syndrome have been documented in England (Braunstein Rosen & Bird 1974) Belgium (François de Laey & Dakir 1974) and the Netherlands (Notting Deutman & van der Werf 1975 Oosterhuis Go Sennema & Graandijk 1976) Juvenile haemorrhagic macular choroidopathy (François de Laey & Dakir) and juvenile haemorrhagic maculopathy (Oosterhuis Go Sennema & Graandijk) have been used as alternative terms of this syndrome Experiences with this group of patients in different geographic areas would be helpful in establishing this clinical entity and its aetiology I therefore felt it would be useful to report the cases seen at the University Eye Hospital in Oulu

Material and Methods

Patients were accepted for the study if they met the following criteria Age below 40 years clear vitreous a haemorrhagic disciform detachment of the macular area and peripapillary chorioretinal scarring In addition four patients had small peripheral atrophic chorioretinal scars

During the last years six patients with juvenile haemorrhagic macular choroidopathy were seen here during different stages of the disease. They underwent a careful ophthalmologic examination including biomicroscopy with a Haag Streit 900 slit lamp and a contact lens recording of the visual fields, fluorescein angiography and red light and red free light photographs of the fundal lesion (Forsius Saari & Nieminen 1976) All patients underwent the routine diagnostic tests used in our uveitis survey (Saari & Miettinen 19), including chest X rays and serological tests for toxoplasmosis Venous blood from four patients was analysed for histoplasmosis complement fixation reaction.

Results

The age of the patients at the initial episode ranged from 12 to 39 years with a mean age of 29 years All were female (Table I) A 28 year old woman (Case 2) with a myopia of -7 25 dioptres in both eyes developed blurred vision in the left eye shortly after a delivery and 11 years later again shortly after a delivery blurred vision in the right eye Another patient (Case 3) had an acute respiratory tract infection just before onset of the eye disease and a similar infection also occurred before the enlargement of the disciform lesion. All of the patients complained of sudden blurring of central vision as the initial symptom metamorphopsia occurred in three cases (Cases 1 2 3)

The right eye was affected with haemorrhagic disciform detachment of the macula in two cases and the left eye in a further two unilateral cases one case was bilateral (Case 2) and one case with haemorrhagic disciform detachment of the macula of the left eye revealed the predisciform stage with small focal yellowish white circumscribed areas of choroidal infiltration in the macula region of the right eye (Case 1)

Peripapillary focal partly pigmented atrophic chorioretinal lesions were seen bilaterally in three and unilaterally in three cases Peripheral atrophic chorioretinal scars occurred bilaterally in one case and unilaterally in three cases There were no flares and no cells in the aqueous and the vitreous was clear in all cases except one with a large haemorrhagic disciform lesion at the macula and some vitreous cells (Case 6)

Table I

Clinical findings in patients with juvenile haemorrhagic macular choroidopathy Occurrence of haemorrhagic disciform detachment of macula (HDD) peripapillary lesions (PPL) and peripheral scars (PS) + (present) − (absent)

Case No	Sex	Age (years)	Eye	Refraction	HDD	PPL	PS	Visual acuity	
								on admission	ultimate
1	F	29	R	+0 5	predisciform	−	+	1.3	2 0
			L	+0 5	+	+	+	0 4	0.25
2	F	28	R	−7 25	+	+	−	0 15	0 25
			L	−7 25	scar	+	+	CF 40 cm	CF 40 cm
3	F	[illegible]	R	+1 75	+	+	+	1 0	CF 5 m
			L	+1 25	−	+	−	1 6	1 6
4	F	39	R	−0.5	−	−	−	1 1	1 1
			L	−0 5	+	+	−	0 4	CF 30 cm
5	F	38	R	−3 5	−	+	−	1 25	1 25
			L	−4 5	+	+	+	0 9	CF 5 m
6	F	12	R	± 0	+	+	−	CF 40 cm	CF 40 cm
			L	± 0	−	−	−	1 1	1 1

All patients were treated with oral corticosteroids with no significant benefit Aspirin® (acetylsalicylic acid) treatment seemed to have a good therapeutic effect in one patient (Case 3) with blood clotting in the central choriocapillaris preceding an exacerbation of the disciform lesion with loss of central vision

The disciform lesion showed a chronic course The progress to the ultimate cicatricial stage took from 6 months to 4 years (in the mean 2 years and 2 months) during which time exacerbations with enlargement of the lesion and recurrent subretinal haemorrhages could be seen The ultimate condition was a greyish white scar with disappearance of oedema and haemorrhages

Table I shows the visual acuity of the patients on admission The visual acuity was markedly reduced in the terminal stage in all eyes with a disciform lesion at the macula two patients had visual acuity of counting fingers at 30–40 cm two patients of counting fingers at 5 m and one patient of 0 25 in the affected eye The patient with bilateral lesions (Case 2) had visual acuity of 0 25 in the right eye and of counting fingers at 40 cm in the left eye with

Fig 2

A Red free photograph shows retinal vessels clearly and outlines choroidal arteries (CA) and veins (CV) in myopic fundus but it does not reveal the greenish pigment ring lesion clearly (arrow)

B Red light photograph showing pigment ring lesion (arrow)

C Fluorescein angiogram showing fluorescence of centre of the lesion

performed through a dilated pupil with a Zeiss fundus camera on black and white panchromatic film In fluorescein angiography we used a Baird Atomic interference filter B 4 and as a barrier a Kodak Wratten filter No 15 In red light photography a Kodak Wratten filter No 29 and in red free light photography a Kodak Wratten filter No 58 were used ICG angiography was performed with the method and equipment developed by Flower (Flower & Hochheimer 1976)

Results

Predisciform stage A patient (Case 1) with haemorrhagic disciform detachment in the left macula revealed focal round whitish dot like areas of *choroidal infiltration* with fuzzy margins in the right macula In fluorescein angiography (Fig 1) the dye appeared in the centre of the whitish area at the time of choroidal filling fluorescence in the infiltrate increased rapidly and became relatively hyperfluorescent when the surrounding choroidal fluorescence subsided In the late phase diffusion of a small amount of dye into the retina was seen After treatment with lasercoagulation the healed scars showed no diffusion of the dye into the retina

A patient with myopia of –7 25 dioptres in both eyes (Case 2) was seen here seven months after delivery she revealed in the right macula a yellowish

white choroidal lesion with dark greenish ring of hyperpigmentation The *pigment ring lesion* was oval smaller than one half disc diameter in size There was no detachment of the overlying retina In red free light photography retinal arteries and veins were visualized and larger choroidal arteries and veins were outlined in the myopic fundus but the greenish lesion was not clearly visualized (Fig 2 A) In a red light photograph the pigment ring lesion was clearly demonstrated (Fig 2 B) In fluorescein angiograms the centre of the lesion showed incipient fluorescence in the arterial phase of the retina and was relatively hyperfluorescent in the late venous phase with diffusion of dye into the pigment halo (Fig 2 C) In ICG angiograms the lesion was located at the site of greatest supply of the short posterior ciliary arteries and large choroidal veins were also prominent in this area (Fig 3) Six months later the pigment ring lesion showed subretinal choroidal neovascularization and was surrounded by subretinal haemorrhages

Disciform stages A patient (Case 3) revealed 10 days after onset of blurred vision a focal *choroidal infiltrate with a circumscribed shallow exudative retinal detachment below the right fovea* Fine radiating folds were seen in the surrounding retina (Fig 4 A) Peripapillary degeneration of the choroid and pigment epithelium was seen (Fig 4 A B and D) A red light photograph revealed below the fovea an area of grouped small degenerative lesions involving the pigment epithelium (Fig 4 B) Fluorescein angiograms demonstrated

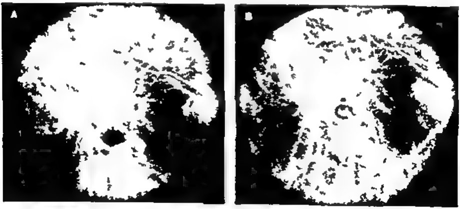

Fig 3

A ICG angiogram showing underfilling of the pigment ring lesion situated in the region of greatest supply of short posterior ciliary arteries

B ICG angiogram 8 later showing filling of large choroidal veins

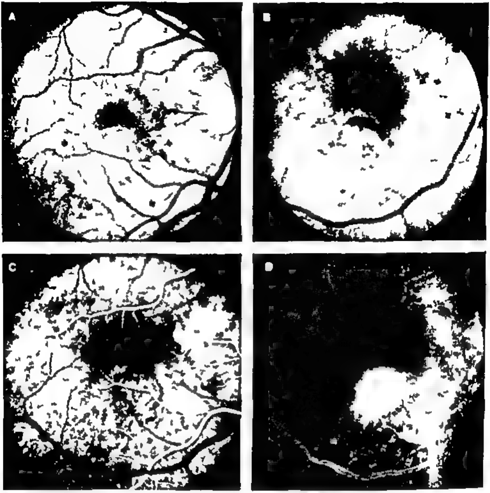

Fig 4

A Red free photograph showing focal choroidal infiltrate with serous disciform retinal detachment (arrows)

B Red light photograph showing degeneration of pigment epithelium at the site of lesion and in peripapillary area (arrows)

C Fluorescein angiogram showing subretinal neovascularization at the site of the lesion

D Late phase with diffuse fluorescence of the lesion

in the lesion new vessel loops in the retinal arterial phase (Fig 4 C) and diffusion of the dye into the surrounding retina in the late phase (Fig 4 D) Three weeks later partial resolution of the pigment ring lesion was seen One month later a new advance of subretinal neovascularization in the direction of the fovea was seen In ICG angiograms the lesion was located at the site of

greatest choroidal supply but the lesion itself remained underfilled during filling of surrounding choriocapillaris Two months later serous detachment of the retina with white subretinal precipitates of variable size in the whole macular area and subretinal blood along the superior margin of the choroidal lesion of one disc diameter were seen (Fig 5 A) Fluorescein angiograms revealed neovascularization corresponding to the extension of the choroidal lesion During acetyl salicylic acid (Aspirin®) treatment resolution of the serous detachment of the retina in one month and disappearance of subretinal precipitates in two and a half months with some depigmentation of pigment epithelium around the lesion were seen (Fig 5 B)

A 39 year old woman (Case 4) was seen here three months after onset of blurred vision showing *serous and haemorrhagic disciform detachment of the retina overlying a yellowish green choroidal lesion* which appeared as a pigment ring lesion in a red light photograph revealing deeper layers of retina The lesion stained intensely with fluorescein Six months later there was a large serous and haemorrhagic disciform detachment of the retina with white subretinal precipitates in an area extending over the optic disc and superior and inferior temporal vessels In ICG angiograms the lesion was situated at the site of greatest choroidal arterial supply but the lesion itself remained unstained throughout the ICG angiogram Fluorescein angiograms showed sub

Fig 5

A Disciform detachment of the macula with white subretinal precipitates and subretinal blood along superior margin of the choroidal lesion (red free photograph)

B Fluorescein angiogram 2 5 months later showing vascularization of the lesion and depigmentation of pigment epithelium around it

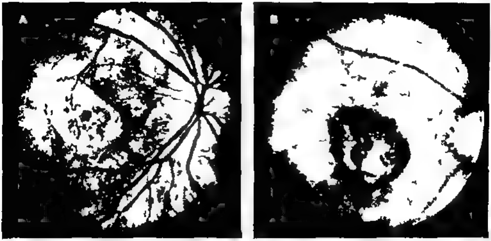

Fig 6

A Red free photograph of a dense disciform scar showing retinal vein (arrow) dipping into the scar

B Red light photograph showing proliferation of pigment epithelium at the borders of the lesion pigment epithelial degeneration in the centre of it and pigment epithelial atrophy around the lesion

retinal neovascularization with rapidly increasing diffuse fluorescence extending from the pigment ring lesion to the fovea

A 38 year old woman (Case 5) was seen here six months after onset of blurred vision in the left eye showing central serous and haemorrhagic disciform detachment of the retina overlying a slightly raised yellowish grey choroidal lesion with subretinal neovascularization Visual acuity of the left eye was 0 ° Despite treatment with systemic steroids for two months the lesion progressed and one year later vision was reduced to counting fingers at 5 m

Scar stage A patient (Case 6) revealed three small round whitish areas of choroidal infiltration in the macular region of the right eye and one and a half years later serous and haemorrhagic disciform detachment of the retina overlying a large choroidal lesion capped by a pigment ring figure and sub retinal neovascularization Resolution of the lesion in the course of six months left a large *dense* focal yellowish grey *subretinal scar* with some vessels within the scar itself (Fig 6 A) A red light photograph revealed proliferation of the pigment epithelium at the borders and pigment epithelial atrophy in the centre of the lesion some depigmentation was seen around the lesion (Fig 6 B)

One patient (Case 2) revealed a *large inactive scar* in the macular area of the left eye 11 years after the appearance of an acute lesion in this eye It

revealed a large area of atrophy of pigment epithelium and total loss of choriocapillaris Fluorescein and ICG angiograms revealed rapid filling of choroidal arteries ; anastomoses between neighbouring short posterior ciliary arteries and location of the lesion at the site of greatest supply of these vessels

Discussion

The nature of the choroidal inflammation in patients with presumed ocular histoplasmosis has hitherto been unknown (Gass 1970) The present fluorescein and ICG angiographic findings suggest a vascular basis for this uveitis entity

In the predisciform stage the primary lesion consists of multifocal whitish punctate choroidal infiltration with hyperfluorescence in the late phase of fluorescein angiogram Clinical findings suggested that intravascular coagula tion in the central choriocapillaris may form the choroidopathy inducing the disciform detachment of the macula (Saari 1977) Fibrin clotting in the chorio capillaris appears as multifocal white areas showing spotty leaks into subretinal space in fluorescein angiography (Cogan 1975) Similar greyish white later yellowish white and in angiograms hyperfluorescent spots were seen after microsphere occlusion of the choriocapillaris (Stern & Ernest 1974)

The disciform stage developed only in the macular area In this study ICG angiograms showed that the choroidal lesion occurred in the region of greatest supply of short posterior ciliary arteries which formed an anastomotic network These arteries unload the blood into the choriocapillaris with a rapid decelera tion of flow which favours the precipitation of clots (Cogan 1975) and concen tration of microspheres injected into the choroid circulation (Alm & Bill 1973 Stern & Ernest 1974)

ICG angiograms in this study revealed that the choroidal lesion remained underfilled throughout the angiogram Intravascular coagulation in the chorio capillaris at the site of the lesion may readily explain this vascular decom pensation

In this study red light photography revealed depigmentation of the pigment epithelium overlying the choroidal lesion and clearly demonstrated the sub sequent pigment ring lesion Choriocapillary occlusion similarly induced the disruption of the overlying pigment epithelium and caused serous disciform detachment of the retina (Stern & Ernest 1974 Cogan 1975)

Fluorescein angiograms revealed subretinal neovascularization corresponding to the extension of the lesion Vascular decompensation at the site of the lesion may induce the focal destruction of the overlying pigment epithelium and sub retinal neovascularization Bleeding from these new vessels may produce the localized haemorrhages seen in this study in all cases

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References

Alm A & Bill A (1973) Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (*Macaca irus*) A study with radioactively labelled microspheres including flow determinations in brain and some other tissues *Exp Eye Res 15* 15–29

Braunstein R A Rosen D A & Bird A C (1974) Ocular histoplasmosis syndrome in the United Kingdom *Brit J Ophthal 58* 893–898

Cogan D G (1975) Ocular involvement in disseminated intravascular coagulopathy *Arch Ophthal (Chicago) 93* 1–8

Flower R W & Hochheimer B F (1976) Indocyanine green dye fluorescence and infrared absorption choroidal angiography performed simultaneously with fluorescein angiography *Johns Hopkins Med Journal 138* 33–42

Forsius H Saari M & Nieminen H (1976) *Comparative fluorescein angiography and red light and red free light photography for examination of vascular changes of the choroid retina and optic nerve head* Paper read in the 5th Congress of the European Society of Ophthalmology 5–9 April 1976 Hamburg

François J de Laey J J & Dakir M (1974) Juvenile hemorrhagic macular choroidopathy *Bull Soc belge Ophtal 167* 664–678

Gass J D M (1967) Pathogenesis of disciform detachment of the neuroepithelium V Disciform macular degeneration secondary to focal choroiditis *Amer J Ophthal 63* 661–687

Gass J D M (1970) *Stereoscopic atlas of macular diseases A funduscopic and angiographic presentation* p 58 Mosby St Louis

Oosterhuis J A Go Sennema A A & Graandijk A (1976) Juvenile hemorrhagic maculopathy *Ophthalmologica 173* 407–409

Saari M (1977) Disciform detachment of the macula I Juvenile haemorrhagic macular choroidopathy *Acta ophthal (Kbh) 55* 525–529

Stern W H & Ernest J T (1974) Microsphere occlusion of the choriocapillaris in rhesus monkeys *Amer J Ophthal 78* 438–448

Woods A C & Wahlen H E (1960) The probable role of benign histoplasmosis in the etiology of granulomatous uveitis *Amer J Ophthal 49* 205–220

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TOXOPLASMIC CHORIORETINITIS AFFECTING THE MACULA

BY

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To study macular changes in toxoplasmic chorioretinitis 41 patients with ocular toxoplasmosis were reviewed Of the 41 patients seven had central large deep pigment ringed scars of congenital toxoplasmosis with poor central vision squint was seen in two and nystagmus in two 32 including 11 cases with a macular lesion had recurrent active toxoplasmic chorio retinitis with a focal yellowish white elevated lesion with indistinct borders mostly at the margin of an old scar and associated with vitreous opacities in all secondary anterior uveitis in 28 macular oedema in 22 papilloedema in 14 and retinal perivasculitis in 16 cases two had rare acquired toxoplasmic chorioretinitis affecting the macula The results show that active toxoplasmic chorioretinitis often causes a widespread intra ocular inflammation with vitritis macular oedema papilloedema retinal perivasculitis and secondary anterior uveitis and suggest a combined treat ment of active lesions with antimicrobial agents and corticosteroids

Key words chorioretinitis – macula – toxoplasmosis – uveitis – vitritis

Ocular toxoplasmosis as a clinical entity has been well defined (Fair 1961 Perkins 1961 Friedmann & Knox 1969 O Connor 1974 Scott 1974) the charac teristic lesion being focal necrotizing chorioretinitis It often affects the central retina causing loss of useful vision (Fair 1961 Friedmann & Knox 1969) The purpose of this study was to describe the macular changes causes of visual disturbance and visual outcome in toxoplasmic chorioretinitis based on cases seen at the University Eye Hospital in Oulu

Material and Methods

The records of 41 patients, 16 of them male, were selected from the case files of the uveitis survey at the University Eye Hospital in Oulu. The patients underwent a careful ophthalmological examination including biomicroscopy with a Haag Streit 900 slit lamp and a contact lens and photography of the fundal lesion with the methods described recently (Forsius, Saari & Nieminen 1976). Patients were included in this study if they met the criteria of toxoplasmic chorioretinitis used by Fair (1961), Friedmann & Knox (1969) and O'Connor (1974). The age of the patients varied from seven to 57 with a mean age of 24.7 years.

Thirty two patients had unilateral and nine (22 %) bilateral chorioretinitis. Thirty eight patients had from one to four focal lesions, one patient had six and one eight focal lesions. The lesions were scattered widely in a bilateral case with five *recurrences*.

Seven patients revealed inactive scars of congenital toxoplasmosis (Fair 1961) and had toxoplasma indirect fluorescent antibody (IFA) or dye test (DT) titres from 1:2 to 1:32 positive; five of them had toxoplasma complement fixation test (CF) titres negative and two had toxoplasma CF 1:4 positive.

Twenty eight patients had a fresh satellite lesion adjacent to an old chorioretinal scar. Additionally four cases with an active juxtapapillary lesion without any old scars were classified as congenital cases because toxoplasma titres did not reveal an acquired infection. These 32 cases were classified as recurrent active toxoplasmic chorioretinitis (Friedmann & Knox 1969). They had the first recurrence from age nine to 50 with a mean age of 21.9 years. Seventeen patients had one recurrence, eight patients had two recurrences, four patients three, one patient five and one patient six recurrences. The average length of all index episodes was 4.3 months with a range from two weeks to 20 months. These 32 patients had toxoplasma DT or IFA titres from 1:4 to 1:256 positive; 18 of them had toxoplasma CF 1:4 negative and 14 from 1:4 *to 1:16 positive*.

Two cases with acute focal necrotizing chorioretinitis, systemic manifestations of acquired toxoplasmosis and highly elevated toxoplasma antibody titres were classified as acquired toxoplasmic chorioretinitis (Saari et al. 1976).

The macular area, as defined by Deutman (1971), was affected in 20 cases (49 %) consisting of seven cases with scars of congenital toxoplasmosis, 11 cases with recurrent acute chorioretinitis and two cases with acquired toxoplasmic chorioretinitis.

The macula alone was affected in 12 cases. Six patients had macular and peripheral lesions; one patient macular and juxtapapillary, and one patient

macular juxtapapillary and peripheral lesions Six patients revealed only juxta papillary 13 patients only peripheral and two patients juxtapapillary and peripheral lesions

Of the 34 patients with an active episode 14 patients were treated with oral corticosteroids alone for one month 18 patients with pyrimethamine (Daraprim®) sulpha and corticosteroids as suggested by Giles (1971) and two without any oral medication Twelve patients underwent an additional laser coagulation (Spalter 1968)

Results

Congenital toxoplasmosis

Seven patients had chorioretinal scars of congenital toxoplasmosis affecting the macula The lesion was a deep focal scar with heavily pigmented and sharply demarcated margins In the centre of the scar the retina and chorio capillaris were destroyed and only large blood filled choroidal vessels were observed against the bare sclera There were three bilateral cases Five patients had a large central scar a congenital coloboma of the macula (Fig 1) of toxo plasmic origin One of them had a bilateral coloboma of the macula and another one a 21 year old woman with idiocy and epilepsy had a coloboma of the macula in the right eye and microphthalmia of toxoplasmic origin in the left eye

There was no evidence of an active inflammation in these eyes Two patients had slight vitreous opacities and there was cataract in the microphthalmic eye

Visual acuity of the affected eye was worse than counting fingers at 1 m in three cases 0 15 in one 0 2 in two cases and 0 4 in one case Five patients

Fig 1
Congenital coloboma of the macula of toxoplasmic origin

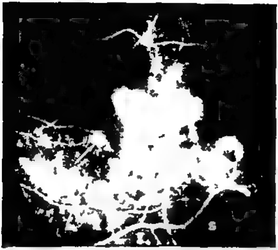

Fig 2
Angiogram showing recurrent active toxoplasmic chorioretinitis (black arrows) adjacent to superior margin of old scar (S) Small active focal lesion (white arrow) near the large one

had normal vision in the better eye The patient with a bilateral coloboma had visual acuity of 0 4 in the better eye The microphthalmic eye was blind Two patients had squint and two nystagmus

Recurrent active toxoplasmic chorioretinitis

Central lesions All cases with recurrent active toxoplasmic chorioretinitis affecting the macula revealed a focal yellowish white elevated lesion with indistinct borders at the margin of an old scar Sometimes tiny active focal lesions were seen near a large one (Fig 2) In some cases the active necrotizing lesion was situated within the margin of the old scar and showed then chronic spread In three cases the recurrent lesion spread from peripheral area into the macula (Fig 2) reducing vision

Inflammatory exudate was cast off from the surface of the focal lesion causing vitreous opacities in all 11 cases In 10 of these 11 cases there was retinal oedema affecting the fovea and in many cases there were preretinal exudates in front of the macula (Fig 3) In many cases the posterior hyaloid membrane was detached and precipitates of inflammatory cells were seen on the posterior face of the vitreous The macular oedema dissolved during the treatment and in some long standing cases left a few pigment dots in the fovea

Of the 11 cases affecting the macula two showed papilloedema four retinal perivasculitis affecting larger retinal vessels particularly the retinal veins

Fig 3
Subacute lesion with precipitates of inflammatory exudates seen as white dots in front of the macula

(Fig 4) nine aqueous flare and cells and some eyes revealed white keratic precipitates

In six cases there were during some recurrence small punctate areas of active retinitis affecting the macula which were associated with minimal oedema and vitreous reaction They caused visual disturbance when they arose in the fovea but healed soon during early treatment with pyrimethamine sulpha and corticosteroids

Fig 4
Angiogram showing papilloedema and retinal perivasculitis associated with recurrent active toxoplasmic chorioretinitis (thick arrows) between old foveal lesion (thin arrow) and papilla

Fig 2
Angiogram showing recurrent active toxoplasmic chorioretinitis (black arrows) adjacent to superior margin of old scar (S) Small active focal lesion (white arrow) near the large one

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Fig 6
Acquired toxoplasmic chorioretinitis with macular oedema and haemorrhages on the optic disc 16 days after onset of blurred vision

blurred vision in her right eye for three days before admission Her visual acuity was 0 5 in the right eye and 1 75 in the left The left eye was normal The right eye showed aqueous cells vitreous opacities and an elevated area of chorioretinitis with white opacification and fuzzy margins (Fig 6) No old chorioretinal scars were seen There were macular oedema exudates and haemorrhages on the optic disc and retinal perivasculitis Treatment with oral deltacortisone for one month was followed by progression of the lesion which healed during the next 12 months with a final visual acuity of 1 5 in the right eye Toxoplasma DT was 1 256 positive and CF 1 16 positive 13 days after the onset of the illness and two weeks later DT was 1 1024 positive and CF 1 64 positive

Discussion

Central vision was markedly reduced in all eyes with central chorioretinal scars of congenital toxoplasmosis Because nothing can be done to these congenital lesions efforts should be concentrated on preventing transmission of acute toxoplasma infection during pregnancy (Saari & Raisanen 1974)

The acute recurrent lesion occurred in most cases at the margin of an old scar This suggests that rupture of the cyst form in the margin of the old scar may liberate trophozoites causing the acute satellite lesion This lends support to the treatment of acute toxoplasmic chorioretinitis with antimicrobial agents pyrimethamine and sulpha Virulent organisms may cause the charac

teristic focal necrotizing lesion seen during all index episodes of the recurrent active cases in this study The retinal punctate lesion seen in this study in six cases during some episode of recurrent active toxoplasmic chorioretinitis affecting the macula may be an incipient stage of a larger focal necrotizing lesion or it may result from low virulence of the organism and good immunologic response of the host These punctate lesions showed a rapid healing during early treatment with pyrimethamine sulpha and corticosteroids

In this study all 32 cases with recurrent active chorioretinitis revealed vitreous opacities and 28 secondary anterior uveitis Vitreous cellular reaction was followed by macular oedema in 22 papilloedema in 14 and retinal perivasculitis in 16 cases This seems to be a conspicuous finding considering that Friedmann & Knox (1969) reported cystic macula in only four and retinal perivasculitis in one of their 63 cases with recurrent active chorioretinitis It is obvious that the inflammatory exudate that is cast off from the surface of the acute focal lesions causes inflammatory cell infiltration of the vitreous vitritis and as a secondary effect macular oedema papilloedema and retinal perivasculitis and secondary anterior uveitis The frequent occurrence of secondary inflammatory reaction with vitritis macular oedema papilloedema retinal perivasculitis and anterior uveitis seen in this study suggests treatment of acute toxoplasmic chorioretinitis with corticosteroids together with antimicrobial agents

Friedmann & Knox (1969) reported visual loss to 20/100 or less in 11 % of their cases with recurrent active toxoplasmic chorioretinitis In this study no one of the 32 patients with recurrent active chorioretinitis suffered visual loss to 0 2 seven patients with macular focal lesions and three juxtapapillary chorioretinitis showed visual loss to 0 3–0 9 and 22 regained normal vision

Acquired toxoplasmic chorioretinitis is rare (Perkins 1973) Two cases were seen in this study They showed clear deterioration when treated with oral corticosteroids suggesting that toxoplasmic chorioretinitis should not be treated with corticosteroids alone

References

Deutman A F (1971) *The hereditary dystrophies of the posterior pole of the eye* pp 12–15 Van Gorcum H J Prakke & H M G Prakke Assen

Fair J R (1961) Clinical eye findings in congenital toxoplasmosis *Surv Ophthal* 6 923–935

Friedmann C T & Knox D L (1969) Variations in recurrent active toxoplasmic retinochoroiditis *Arch Ophthal (Chicago)* 81 481–493

Forsius H Saari M & Nieminen H (1976) Comparative fluorescein angiography and red light and red free light photography for examination of vascular changes of the

choroid retina and optic nerve head *5th Congress of the European Society of Ophthalmology* 5–9 April 1976 Hamburg

Giles L L (1971) Pyrimethamine (Daraprim) and the treatment of toxoplasmic uveitis *Surv Ophthal 16* 88–91

Perkins E [redacted] (1961) *Uveitis and toxoplasmosis* pp 50–116 J & A Churchill London

Perkins E S (1973) Ocular toxoplasmosis *Brit J Ophthal 57* 1–17

O Connor G [redacted] (1974) Manifestations and management of ocular toxoplasmosis *Bull N Y Acad Med 50* 192–210

Saari M & Raisanen [redacted] (1974) Transmission of acute toxoplasma infection The survival of trophozoites in human tears saliva and urine and in cow s milk *Acta ophthal (Kbh) 52* 847–852

Saari M Vuorre I Nieminen H & Raisanen S (1976) Acquired toxoplasmic chorioretinitis *Arch Ophthal (Chicago) 94* 1485–1488

Scott E H (1974) New concepts in toxoplasmosis *Surv Ophthal 18* 255–274

Spalter H F (1973) A therapeutically oriented uveitis survey In Aronson S [redacted] Gamble C N Goodner E K & O Connor G R Eds *Clinical Methods in uveitis* pp 75–85 Mosby St Louis

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VARIA

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Will be held November 10–12 1977 in Iowa City The topics will be Perimetry in Neuro ophthalmology (Frisen Sweden) Pupils (Thompson Iowa City) Disc swelling (Glaser Miami) Visual evoked responses (Glaser Miami) CT scanning in Neuro ophthalmology (Sanders) For further information write to Dr H Stanley Thompson Department of Ophthalmology University of Iowa Iowa City Iowa 52242

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LYMPHOMA AND OTHER LYMPHOID LESIONS OF THE ORBIT (II)

BY

JØRGEN KLEENER

The incidence survival rate and causes of death of patients with orbital lymphomas and other lymphoid lesions of the orbit in Denmark during the period 1943–62 inclusive were studied by means of a clinico pathological analysis In the period examined the incidence of histologically verified primary orbital tumours was 0 06 ‰ The incidence of primary orbital lymphomas and lymphod lesions was at least 0 012 ‰
These can be histologically divided into 3 categories benign indeterminate (intermediary) and malignant The present study confirms the relevance of this classification as there is a definite relationship between the histological diagnosis and the clinical survival rate.
For the patients in question, the chances of dying of a universal malignant disease were approximately 10^3 times greater than in the normal Danish population

Key words orbit – tumours – orbital lymphoma – lymphoma – reactive lymphoid hyperplasia – lymphoproliferative disease

The purpose of this study was to shed some light on the histologically and clinically somewhat mysterious lymphomas of the orbit

The incidence survival rate and causes of death of patients with orbital lymphomas and lymphoid lesions of the orbit in Denmark during the period 1943–62 inclusive were studied by means of a clinico pathological analysis

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Material

The present study consisted of a clinico histopathological analysis of all *primary histologically diagnosed* lymphomas or lymphoid tumour like lesions of the orbit in Denmark during the period 1943–62 (inclusive)

This 20 year period has been chosen because it coincides with the foundation of the card index of the Eye Pathology Institute Furthermore the registration of all malignant tumours in Denmark at the Cancer Register had started one year prior to this period The minimal period of follow up was 10 years 65 cases were obtained In 9 cases the actual histological specimen was missing but a histological description was available with the case notes Four cases were omitted as they were in fact conjunctival lymphomas

Altogether there were 52 *cases with histologically verified* lymphoma or lymphoid tumour like lesions of the orbit during the period 1943–62 inclusive

All the histological preparations have been revised several times by means of the usual haematoxylin eosin stained preparations and special stains including PAS Unna Pappenheim and reticulum stain

The cases were divided histopathologically into 3 categories

1 Reactive lymphoid hyperplasia benign (lymphoid pseudotumour)
2 Lymphoid lesions of indeterminate nature (intermediary group)
3 Malignant lymphomas

Ad 1 In this study only the group reactive lymphoid hyperplasia is included this means that other inflammatory tumour like lesions (17 inflammatory pseudotumours) are excluded

Ad 2 As the name indicates this category comprises those lymphoid lesions which cannot be placed in either group 3 or in group 1 One of the cases has previously been described (Kleener 1975) as being of the lymphoproliferative type

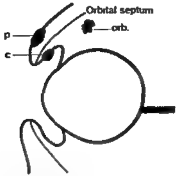
After the limitation of the material the case records of all the 52 patients were reviewed Inquiries were made at the National Register the Central Card Index for deceased persons at the Ministry of Health and at certain local registry offices In this way information regarding the date of death (1973) and the death certificates of 39 patients were obtained The death certificate of one patient could not be obtained Twelve patients were still alive in 1973

In the majority of cases it was possible to confirm that the death certificate contained either a clinical or a post mortem diagnosis

A considerable number of clinical and post mortem diagnoses including lymphosarcoma reticulosarcoma lymphoid and myeloid leukaemia and Hodgkins disease were given

Demarcation and definitions of orbital lymphoid tumours appears in Fig 1

Demarcation of orbital lymphoid tumours



p palpebral tumours
c conjunctival tumours
orb orbital tumours situated behind the orbital septum.

Fig 1
Demarcation of orbital lymphoid tumours

In two cases the tumour is described as originating from the fornices but prominating forwards subconjunctivally These are included in the material as it must be assumed that in both cases there is extension behind the orbital septum

Results

Frequency the incidence of primary orbital lymphomas or lymphoid lesions

The average population in Denmark during the period 1943–62 inclusive was 4 312 mill The incidence of histologically verified primary orbital tumours (263 in all) was 0 06 ‰ (Eldrup Jorgensen 1970) The incidence of the 52 histologically verified primary orbital lymphomas/lymphoid lesions was 0 012 ‰

Sex

The sex distribution is 28 ♂ and 24 ♀ In other words there is no sex difference (see Table I)

Table I
Sex distribution of patients with orbital lymphoid lesions

	Benign	Intermediary	Malignant	
♂	10	9	[illegible]	28
♀	9	11	4	24
	19	20	13	52

Clinical localisation

This is judged from the clinical description of the position of the tumour in the orbit Six are situated retrobulbarly 34 are localized *above* and 8 under the lid opening (Table II)

Clinical symptoms at the first examination

In three cases information concerning symptomatology is missing In the majority of the patients several symptoms are described 55 % of the patients had exophthalmus as one of the symptoms (27 out of 49) (Table III)

Duration of symptoms before biopsy

In four cases information concerning the time of onset is lacking (Table IV) 63 % had first symptoms less than six months before the date of biopsy 85 % had first symptoms less than one year before the date of biopsy

Table II
Clinical localisation of orbital lymphoid lesions

Upper temporal quadrant	20
Upper quadrant without further information	14
Lower quadrant	8
Retrobulbar	6
No information on localisation	2
Other*	2

* One situated nasally and one situated corresponding to the whole of the orbit around the eyeball

Table III

Clinical symptoms at first examination (before biopsy)

	Number of patients with the described symptom
Exophthalmus	27
Swelling of the upper eyelid	14
Nodule/tumour or swelling of eye surrounding	11
Conjunctival complaints	10
Double vision	4
Ptosis	3
Dislocation of eyeball	1
Reduced vision	1

The conjunctival complaints consist of lacrimation or of a foreign body sensation

Age at the time of biopsy

At the time of biopsy 77 % of cases were aged between 50–80 years. The average age at the time of biopsy was 57.2 years. The youngest patient was one year and the oldest 78 years.

The average age for the histologically *benign* group was *52.8 years*. The youngest was 15 years and the oldest 77 years.

The average age for the histologically *intermediary* group was *60.7 years*. The youngest was one year and the oldest 78 years.

The average age for the histologically *malignant* group was *58.2 years*. The youngest was 4 years and the oldest 78 years (Table V).

Table IV

Duration of disease before biopsy as judged from the patient's first observation

0–14 days	2
14 days–1 month	5
1–3 months	12
3–6 months	11
6 months–1 year	11
1–2 years	5
> 2 years	2

Table V
Age at biopsy as compared with the histological diagnosis

Histological diagnosis	Age < 40	40–49	50–59	60–69	70–79	≥ 80
Malignant	2	0	4	2	5	0
Intermediary	2	0	2	11	5	0
Benign	3	5	4	3	4	0
Total	7	5	10	16	14	0

Histological diagnosis

19 cases of the "benign" group were discovered, 20 cases of the so called "intermediary" group, 13 cases of the "malignant" group (Table I).

Survival after biopsy (Table VI)

Twenty two patients survived more than 10 days after the biopsy. Nine patients survived less than one year following biopsy. Five of these were histologically malignant tumours of the orbit. One was histologically benign and three were intermediary.

Table VI
Survival after biopsy of patients suffering from orbital lymphoid lesions

Under 3 months	5
3–6 months	1
6–12 months	3
1–2 years	0
2–3 years	0
3–4 years	2
4–5 years	3
5–6 years	1
6–7 years	0
7–8 years	1
8–9 years	1
9–10 years	1
> 10 years	22

Table VII

Patient survival rate as compared with an estimated normal population

		Duration of observation period in months						
		12	24	36	48	72	96	120
	A	84.3	72.7	72.7	66.7	59.1	47.5	41.9
Total tumours	B	5.1	6.2	6.2	6.6	6.9	7.0	6.9
	C	97.6	95.0	97.3	89.4	83.5	76.4	69.0
	A	62.7	33.4	33.4	33.4	24.4	16.6	9.9
Malignant	B	13.4	13.1	13.1	13.1	12.5	10.6	8.2
	C	97.0	93.8	90.4	86.8	79.4	71.2	62.8
	A	89.5	79.2	79.2	69.8	63.8	43.2	38.6
Intermediary	B	7.0	9.9	9.2	10.6	10.9	11.3	11.0
	C	97.3	94.5	91.6	88.5	82.1	74.8	66.9
	A	94.6	94.6	94.6	89.2	78.9	73.6	63.5
Benign	B	5.3	5.3	5.3	7.2	9.4	10.1	10.7
	C	98.2	96.3	94.3	91.0	87.3	82.0	76.0

A Calculated % survival amongst the patients
B Standard deviation (%)
C Calculated % survival for corresponding population (sex, age, date of birth)

The calculated percentage patient survival is based on the assumption that there is a constant mortality in the intervals. $\pm$ 2 × standard deviation represent 95 % confidence limits for the true survival amongst the patients.

Of the 22 patients who survived more than 10 years following biopsy, 13 were benign, 7 were intermediary and 2 were malignant.

When compared with the survival rate of a similar population, the histologically *malignant* group showed a significant higher mortality rate after a 1 year observation period.

A significant higher mortality rate for the *intermediary* group was found after an 8 year observation period. The mortality rate of the *benign* group corresponded to that of a normal Danish population of the same sex, age and date of birth (Table VII and Fig. 2).

Cause of death

Table VIII shows the cause of death divided according to the three histological groups. From the statistics of the Cancer Register the incidence of malignant

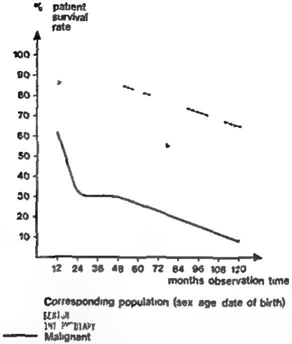


Fig 2

The curve for the survival rate of the normal population is estimated from age sex and date of birth for the total material As can be seen from Table VII an independant normal population survival rate curve belongs to each of the three histological sub groups These are not represented here as they lie very close to the curve for the total material

Table VIII

Cause of death patients with orbital lymphoid lesions

Cause of death	Malignant	Intermediary	Benign	
Unspecified	2	4	8	14
Cancer lues (I case)	1	[illegible]	[illegible]	5
Malignant systemic disease	9	10	1	20
No death certificate		1		1
Still alive	1	3	8	12
	[illegible]	20	19	52

systemic disease" in Denmark during the 4 year period 1958–62 was found to be 0 39 ‰ (Clemmesen 1974) In this context malignant systemic disease" is understood to be a malignant tumour of lymphoid or haemopoietic tissue (lymphosarcoma reticulosarcoma malignant lymphoma lymphogranulomatosis maligna multiple myeloma lymphatic leukaemia myeloid leukaemia mycosis fungoides) The incidence of " lymphoma orbitae is as previously mentioned 0 012 ‰

Of the 52 patients in the material 20 patients died of malignant systemic disease i e 38 % The chance of dying of a malignant systemic disease once an orbital lymphoma has been diagnosed is therefore approximately 10^3 times greater than within the normal Danish population 69 % of the histologically malignant group died of a malignant systemic disease 50 % of the histologically intermediary group died of a malignant systemic disease

Discussion

For definitions descriptions and illustrations of lymphomas the reader is referred to Histological and Cytological Typing of Neoplastic Diseases of Haematopoietic and Lymphoid Tissues WHO International Histological Classification of Tumours No 14 1976

In addition a new classification of non Hodgkin s lymphomas has been put forward by Bennett et al (1974) and a further one by Dorfman (1974) Yet another classification the so called Kiel Classification has been put forward by Gerard Marchant Hamlin Lennert Rilke Stansfeld & Unnik (1974)

Material of orbital lesions has to be supplemented by immunological investigations before further re classification can take place In this preliminary report therefore the more simple classification is used

Several hypotheses and classifications of orbital lymphoid lesions have been put forward

Stark & Thiel (1970) divide the orbital lymphoid tumours into two groups Firstly the isolated orbital tumours and secondly those which are a part of a systemic disease in the lymphatic tissue This classification seems to be less logical than one based on a histological diagnosis

Damaske Hartung & Muller (1972) divide the lymphoid lesions into sarcomas systemic diseases and infectious conditions

Sugarbaker & Craver (1940) found 1 % of primary extra nodal lymphomas localized in the orbit and 1 5 % of patients with a universal lymphoma showed involvement of eyelid conjunctiva and orbital tissue

Yehuda & Hallon (1971) found 162 patients with primary ocular or adnexal tumours Of these 56 were extraocular primary orbital tumours (during the period 1944–63) There were 12 benign and 44 malignant tumours Four of the benign belonged to the group lymphoid lesions Of the 44 malignant tumours 14 were malignant lymphomas without any sign of systemic disease A systemic disease of which five patients died developed from 1–7 years later in six patients

Morgan (1973) has followed up 60 orbital lymphoid lesions They were divided into benign lymphomas and lymphosarcomas and the course followed for more than five years with regard to the development of a generalized disease The main weakness is the lack of relevant statistical evaluation

It is altogether characteristic for this difficult field that no studies exist which satisfactorily illustrate the incidence and survival of these tumours Certain collective studies are to be found amongst others by Lane (1922) and Schrech s (1939) but without any correlation to a permanent population

The most frequent site for *lymphoid lesions in the orbit regardless of the* histological type is the area around the lacrimal gland Mortada (1961) maintains that this is because in the orbit lymphatics are only to be found in the lacrimal gland (Ingalls 1953)

The survival rates show that there is no difference in survival rate between the benign lymphoid lesion and a corresponding normal population

After 8 year observation period the intermediary group shows a significant higher mortality rate compared with a corresponding normal population The malignant lesions show a significant mortality rate after only a 1 year observation period On the basis of this alone it seems reasonable to classify the benign lymphoid lesions on their own and the justification for maintaining the term benign seems to be clear These tumours apparently arise spontaneously and show no tendency towards any connection with the generalized diseases which reduce the survival rate On the other hand the intermediary and the malignant tumours appear to have a specific connection with generalized diseases or defects (of immunological character) of the lymphoid and haemopoietic tissue The precise nature of this connection for the time being remains open The demonstration by Morgan that diastase resistent PAS positive intranuclear inclusions which are assumed to be composed of glycoprotein of 18 S type (Dutcher Fahey bodies) count against the development of a generalized disease agrees with the division employed in the present material where demonstration of Dutcher Fahey bodies suggests that the tumours be placed in the histologically intermediary group

However the massive mortality of malignant systemic disease – approximately 10^3 times that of the normal population – supports the fact that orbital

lymphoid lesions which are not of a definite benign nature can be taken as an early warning of a later generalized disease None of the diagnostic methods available at the present time can demonstrate this at such an early stage

It is important to note that conditions in the orbit in many ways are relatively unknown There is no clarification of the question as to whether there are any functionally operative lymphatics in the orbit The drainage conditions in connection with neoplasms support the supposition that functioning lymphatics do *not* exist

The present examination demonstrates that it is also statistically justifiable to maintain the distinction between benign intermediary and malignant lymphoid tumours

Histologically these tumours probably belong to one of the most difficult fields in orbito ocular histopathology It is only in the more recent years that the subgroups have begun to be distinguished so giving a better clinical guidance The *purely malignant* tumours are the easiest group to diagnose The decisive factor is that they consist of lymphocyte cells ranging from well differentiated cells to very pleomorphic malignant cells Other cell types are rarely seen except in the case of certain types of Hodgkin s disease

Up to now the *benign tumours* have been regarded as being the most frequent, and this remains so when all the variants of inflammatory lesions are included (see material) If the group lymphoid pseudotumours or reactive lymphoid hyperplasia" is considered alone then it will be seen that it is the intermediary group which is the largest one A heterogenous collection of cell types – lymphocytes plasma cells reticulum cells and histiocytes – is characteristic for reactive lymphoid hyperplasia All the cells are well differentiated and lymphoid follicles are occasionally to be found

Those tumours that cannot definitely be placed in either the malignant or the benign group are included in the *intermediary* group (Often a pure proliferation of mature lymphocytes is seen) Histologically it is now apparent that the presence of certain eosinophilic intranuclear inclusion bodies – Dutcher Fahey bodies – (P A S positive) indicates that for the time being there is no question of a neoplasm but rather of an immune reaction about which nothing further is known It is recommended that patients who have developed such a tumour be followed up with regard to the development of a universal disease

The therapeutic consequences of the diagnosis lymphoma or lymphoid lesion of the orbit are not considered in the present study As shown however the diagnosis intermediary or malignant lesion should always be followed by a thorough general clinical examination Usually in the initial stage no sign

of a generalized disease will be found and for this reason the patient should be seen regularly with regard to the possible development of a general malignant systemic disease Local treatment in the form of radiotherapy with tumour doses as for malignant lymphoma or systemic treatment with prednisone are among the most usual forms of therapy

References

Bennett Farrer Brown Henry & Jelliffe (1974) Classification of Non Hodgkins Lymphomas *Lancet 2* 405–406

Clemmesen J (1974) Statistical staudies in malignant neoplasms in Denmark 1943–67 *Acta path microbiol scand Suppl 247* Section A

Damaske E Hartung W & Muller K M (1972) Zur Diagnostik und Therapie der Orbitatumoren *Klin Mbl Augenheilk 160* 411–419

Dorfman R F (1974) Classification of Non Hodgkins Lymphomas *Lancet 1* 1295–1296

Eldrup Jorgensen P (19?0) Primary histologically confirmed tumours in Denmark 1943–196? *Acta ophthal (Kbh) 48* 657–666

Gerard Marchant Hamlin Lennert Rilke Stansfeld & van Unnik (1974) Classification of Non Hodgkins Lymphomas *Lancet 2* 406

Ingalls R G (19?3) Tumors of the orbit and allied pseudo tumors Charles C Thomas Springfield USA

Kleener J (1975) Lymphoma and other lymphoid lesions of the orbit *Acta ophthal (Kbh) 53* ?10–216

Lane L (19?2) Tumors of the lacrimal gland *Amer J Ophthal 5* 425

Morgan Gwyn (1975) Proc 2nd Int Symp on orbital disorders *Mod Probl Ophthal 14* 355–360

Mortada A (1961) Orbital reticulum cell sarcoma *Brit J Ophthal 45* 365–376

Schreck (1939) Orbitale tumoren *Klin Mbl Augenheilk 103* 1

Stark N & Thiel H D (19?0) Lymphatic tumors in the eye region *Klin Mbl Augenheilk 157* 308–326

Sugarbaker & Craver (1940) Lymphosarcoma *J amer med Ass 115* 17–?3

WHO *International Histological Classification of Tumours* No 14 (19?6) Histological and Cytological Typing of Neoplastic Diseases of Haematopoietic and Lymphoid Tissues

Yehuda G A & Hallon W F (1971) Primary orbital tumors *Amer J Surg 1??* 727–731

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THE INFLUENCE OF STIMULUS DURATION ON THE HUMAN D C REGISTERED c WAVE

A Quantitative Study

BY

OLA TEXTORIUS

The *c* wave of the human ERG was studied at different stimulus durations with a d c technique which permitted stable and reproducible recordings With increasing stimulus lengths the implicit time increased up to a maximum of about 5 5 s Also the amplitude of the *c* wave rose. However it was influenced by positive and negative off effects seen in most volunteers and at several stimulus lengths superimposed upon the peak of the *c* wave This fact must be considered when developing a standardized method for measuring the *c* wave amplitude proper

Key words electroretinography – clinical method – *c* wave – retina – pigment epithelium

The properties of the *b* wave of the ERG including its reactions to changes in stimulus duration have been repeatedly investigated since the early days of electroretinography (Gotch 1903 Brucke & Garten 1907 Einthoven & Jolly 1908 Motokawa & Mita 1942 Muller Limmroth 1953 and others) There is less information concerning *c* wave characteristics Early investigators (Einthoven & Jolly 1908 Jolly 1909) (frog) noted the dependence of *c* wave amplitude upon stimulus duration More detailed studies were performed by Muller Limmroth (1953) (rabbit) and Noell (1953) (rabbit) Both authors reported longer implicit times with more extended flashes Noell (1953) found larger *c* waves after longer stimuli and demonstrated an off effect, superimposed upon the *c* wave

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at the termination of long flashes The *c* wave originates mainly in the pigment epithelium – receptor complex (Steinberg Schmidt & Brown 1970 Oakley & Green 1976 and others) In intracellular recordings from the pigment epithelium (Schmidt & Steinberg 1971) (cat) the amplitude of the response rose with increasing flash durations These findings were confirmed by Niemeyer (1973 1975)

With the d c ERG technique initially described by Knave Nilsson & Lunt (1973) and further developed by Skoog & Nilsson (1974a b) and Skoog (1974 1975) stable and reproducible recordings of the human *c* wave can be obtained without the aid of general anaesthesia In those registrations 1 s light stimuli were used since such a duration was considered realistic in connection with clinical examinations of patients The relationship between stimulus intensity and *c* wave amplitude the cyclic behaviour of the *c* wave and the effect of ethyl alcohol on the *c* wave were investigated in man (Skoog & Nilsson 1974a b Skoog 1974) A similar method was used in a paper by Taumer Rodhe Wichmann & Rover (1976) where in the results of one experiment they point out the influence of the stimulus duration and the off effect on the human *c* wave However the *c* wave amplitude remained rather constant when measured from the preceding trough Recently the off responses of the human ERG were studied in detail in our laboratory (Skoog Welinder & Nilsson 1977) The present investigation concerns a quantitative study of the dependence of the human *c* wave on stimulus duration with special reference to the influence of different superimposed off responses

Material and Methods

Six healthy volunteers (four women two men) aged 20–32 years were studied None was under the influence of drugs or stimulants

The recording procedure was described by Knave Nilsson & Lunt (1973) and modified by Skoog & Nilsson (1974a b) and by Skoog (1974 1975)

Before the registrations the pupils were dilated to 8 mm or more with 0 5 % tropicamide (Mydriacyl®) and 10 % phenylephedrine hydrochloride (metaoxedrine Neosynephrine®) After topical anaesthesia a scleral contact lens was applied to one of the eyes The lens was filled with Methocel® Two polyethylene tubes were connected to the lens One containing saline ended in a beaker with saline the surface of which was located 20 cm below the level of the eye The slight suction effect obtained prevented the lens from sliding on the eye The other tube served as a saline agar bridge to the recording electrode The reference electrode was connected by a similar bridge to a

Methocel® filled plastic chamber on the forehead above the examined eye One arm was grounded After these preparations the volunteer was left in darkness for at least 30 min before starting the registrations

The impulses from the examined eye passed via matched calomel half cells into a low drift d c amplifier The signals were then fed into a Tandberg analogue tape recorder and after low pass filtering 220 Hz cut off 18 dB/octave) into a Hewlett Packard 5480 S signal analyzer During the recording procedure the volunteer and the electrodes were protected from electrical disturbances by a wire net cage Stimulus light was produced by a 150 watt ozone free Osram XBO xenon lamp After passing heat reflection and heat absorbing filters (Zeiss) as well as neutral density filters (Balzer) the light was transmitted through a quartz fibre optics (Schott) to the eye

During recordings the free eye fixated a very weak deep red light in the ceiling

Both eyes were studied with the aid of a corneal microscope after the registrations No corneal abrasions were found Applanation tonometry was performed before the application of the lens and immediately after its removal There were no significant changes in intraocular pressure

The intensity of light eliciting a single flash *b* wave (threshold at 30–40 μV) in a normal eye is referred to as log relative intensity 0 Log relative intensity 4 0 was used in the experiments Light flashes of successively increasing duration were employed in a series (0 13 0 25 0 5 1 2 4 8 and 16 s) Four responses at each stimulus duration were averaged displayed on the oscilloscope screen and then photographed The interval between the flashes was 30 s (0 13 0 25 0 5 1 s stimuli) 45 s (2 4 s stimuli) 90 s (8 s stimuli) or 120 s (16 s stimuli) Two series of light flashes were presented to the eye at each experimental session A pause was inserted between the series in order to avoid a phase dependent influence on the results A total of 14 series was performed

The *c* wave amplitude was measured from the iso electric line as well as from the trough preceding the *c* wave and to the highest peak in the region of the *c* wave Also the implicit time of the *c* wave was measured from the photographs

Results

In Fig 1 *c* wave amplitude measured from the iso electric line is plotted against stimulus duration (logarithmic scale) The amplitude rises with increasing durations up to 4 s The initial phase of the curve has a different

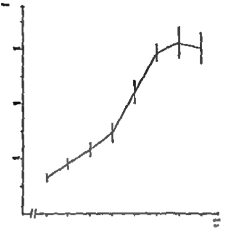

Fig 1
The relationship between *c* wave amplitude measured from the iso electric line and stimulus duration (logarithmic scale) (Means and standard error of the mean from 14 experiments)

slope than the part between 1 and 4 s At 4 8 and 16 s there is no statistically significant difference between the *c* wave amplitudes

In Fig 2 the same relationship is again shown but with stimulus duration on a linear abscissa The increase in *c* wave amplitude is most pronounced at short flash durations The curve then becomes more flattened reaching a plateau after 1 s

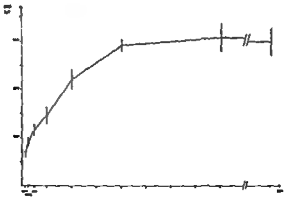

Fig 2
The relationship between *c* wave amplitude measured from the iso electric line and stimulus duration (linear scale) (Means and standard error of the mean from 14 experiments)

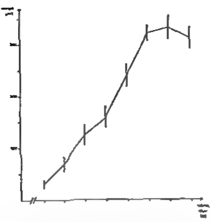

Fig 3

The relationship between *c* wave amplitude measured from the bottom of the preceding trough and stimulus duration (logarithmic scale) (Means and standard error of the mean from 14 experiments)

The relationship between *c* wave amplitude measured from the bottom of the preceding trough and stimulus duration is seen in Figs 3 and 4 (logarithmic and linear abscissa respectively) The shape of the curves is essentially the same as when the amplitude is measured from the iso electric line

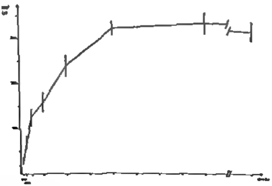

Fig 4

The relationship between *c* wave amplitude measured from the bottom of the preceding trough and stimulus duration (linear scale) (Means and standard error of the mean from 14 experiments)

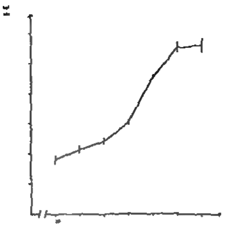

Fig 5
The relationship between implicit time of the c wave (measured from on to c wave peak) and stimulus duration (logarithmic scale) (Means and standard error of the mean from 14 experiments)

The relationship between implicit time of the c wave and stimulus duration is illustrated in Figs 5 and 6 (logarithmic and linear scale respectively) The implicit time increases with longer stimuli and seems to have reached a plateau of about 5 5 s at stimulus duration 8 s

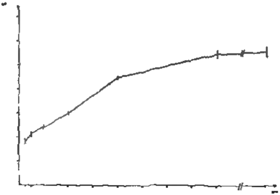

Fig 6
The relationship between implicit time of the c wave (measured from on to c wave peak) and stimulus duration (linear scale) (Means and standard error of the mean from 14 experiments)

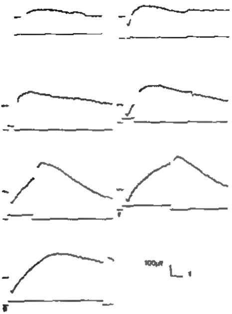

Fig 7

The d c recorded human ERG in response to stimulus durations a 0 13 b 0 25 c 0 5 d 1 e 2 f 4 and g 8 s Stimulus intensity 4 0 log units above *b* wave threshold

A typical series of ERG recordings from a volunteer with pronounced off effects is shown in Fig 7 In the present study most recordings were of this type The illustrated stimulus durations range from 0 13 to 8 s With stimulus durations of 1 s and longer clear fast off effects are seen a positive and then a negative deflection These are in turn followed by changes in the form of an increase and then a decrease of the steepness of the slope most clearly seen in Fig 7 g These changes look like slow off effects The shape of the curves indicates that the same phenomena are also present at the short stimulus durations (0 13–0 5 s) The positive slow off effect being superimposed upon the *c* wave seems to contribute to its amplitude at least at flash durations 2 and 4 s The trough preceding the *c* wave is deep in this series of registrations

The ERG recordings from another volunteer shown in Fig 8 serve as an example of the rather marked individual differences The off effects are far less conspicuous than in Fig 7 but can still be identified at most stimulus durations The trough does not extend below the iso-electric line

The other experiments fully confirmed the above findings

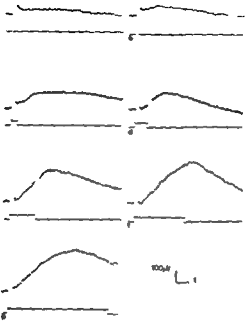

Fig 8

The d c recorded human ERG in response to stimulus durations a 0 13 b 0 25 c 0.5 d 1 e 2 f 4 and g 8 s Stimulus intensity 4 0 log units above *b* wave threshold

Discussion

Gotch (1903) and Einthoven & Jolly (1908) in recordings from frog eyes observed that a long stimulus produced a higher *b* wave than a short one In the study by Muller Limmroth (1953) (frog) the *b* wave amplitude was constant when the stimulus duration ranged between 0 2 and 1 0 s When the flash duration was decreased below 0 2 s both amplitude and rise time of the *b* wave were reduced A *d* wave could be identified when the stimulus was longer than 0 2 s Motokawa & Mita (1942) investigated the human ERG When the stimulus duration was increased the amplitude of the *b* wave rose to a certain constant value which was characteristic of the chosen stimulus intensity Further studies on dark adapted human eyes were published by Alpern & Faris (1956) The *b* wave amplitude rose with increasing stimulus durations At a given flash intensity the response appeared to reach a maximum at a certain stimulus duration which was shorter for bright than for weak stimuli The *a* wave

behaved similarly Johnson & Bartlett (1956) (man) did not observe any changes in the *b* wave latency in response to stimuli of different durations but at low intensities the implicit time was longer with increasing flash lengths The *b* wave amplitude was found to vary in about the same way as described by Alpern & Faris (1956) also confirmed by Burian (1970) (man)

Considerably fewer studies concerning the relationship between *c* wave characteristics and stimulus duration have been published According to the recordings shown by Brucke & Garten (1907) the peak of the secondary rise or the *c* wave is reached earlier when a relatively short flash is used than when a longer stimulus is employed (frog) Einthoven & Jolly (1908) were able to observe a *c* wave only when either the intensity or the duration of the stimulus exceeded a certain limit (frog) Jolly (1909) (frog) found a higher *c* wave amplitude with a 13 2 s stimulus than with a short flash of 0 09 s duration In experiments on rabbits Muller Limmroth (1953) described a continuous decrease of the implicit time of the *c* wave when the length of the stimulus was shortened Noell (1953) (rabbit) observed that the peak of the *c* wave was progressively delayed up to a maximum of 3–10 s with increasing stimulus durations which also produced higher *c* wave amplitudes as may be seen in the illustrated registrations An off effect was superimposed upon the *c* wave at the termination of long flashes Steinberg Schmidt & Brown (1970) using a microelectrode technique were able to demonstrate in the cat eye that the intracellularly recorded potential of the pigment epithelium behaved similarly to the *c* wave of the local ERG With increasing stimulus duration the peak amplitudes of both parameters rose reaching a plateau when the flash length exceeded 2 4 s (Schmidt & Steinberg 1971) When the amplitude of the pigment epithelial response was plotted as a function of log duration of the stimulus at least two growth periods were seen one at brief durations (10–50 ms) and another one at longer durations Niemeyer (1973 1975) recorded the intraretinal ERG and the intracellular responses of the isolated perfused cat eye In the intraretinal ERG tracings both the amplitude and the implicit time of the *c* wave were found to increase with longer stimuli The intracellular recordings confirmed the findings of Steinberg Schmidt & Brown (1970) and Schmidt & Steinberg (1971) From the animal experiments and from one experiment on the human *c* wave published by Taumer Rodhe Wichmann & Rover (1976) it is evident that short stimuli do not give the full amplitude of the *c* wave and that the off effect also may influence the *c* wave

Recently off responses of the human ERG were studied by Skoog Welinder & Nilsson (1977) After a positive and then a negative fast wave a slow positive peak and a slow negative trough occurred which in turn was followed by a maximum after about 45 s corresponding to the fast EOG transient The first

four off-responses were termed *d* *f*- *g*- and *h* waves respectively The positive slow off effect seen in the present registrations (the *g* wave according to Skoog Welinder & Nilsson 1977) may augment the *c* wave amplitude at least after 2 and 4 s flashes For this reason it is not possible to identify the exact peak of the *c* wave proper but the amplitude must be measured to the maximum peak knowing that this value is more or less influenced by the positive g wave A similar pattern was reported by Taumer Rodhe Wichmann & Rover (1976) At stimulus durations 0 13 0 25 0 5 and 1 s a slow negative off effect (the *h* wave according to Skoog Welinder & Nilsson 1977) might reduce the peak of the *c* wave It is tempting to interpret the relative flattening beginning about 0 5 s after off of the registration in Fig 7 c in this way At flash durations 4 8 and 16 s the log duration – amplitude curve (Fig 1) seems to have reached a plateau The maximum implicit time of the *c* wave was about 5 5 s (Figs 5 and 6) Although in our experiments stimulus durations between 4 and 8 s were not used one would expect the *c* wave amplitude to grow with increasing stimulus durations up to 5 5 s That the amplitude at 8 and 16 s is not significantly higher than at 4 s is probably explained by the fact that the off effects including the positive g wave at 8 and 16 s stimulus durations are superimposed upon the descending limb of the *c* wave and thus do not augment the peak amplitude Consequently the three phases of the log duration – amplitude curve (Fig 1) which occur between 0 13 and 1 s 1 and 4 s and between 4 and 16 s respectively may be explained at least partly by the presence or absence of different off effects superimposed on the *c* wave peak Taumer Rodhe Wichmann & Rover (1976) using stimulus durations from 1 to 30 s found a constant amplitude of the *c* wave when measured from the preceding trough In their illustrated experiment the peak of the *c* wave reaches above (10 s) up to (15 s) and slightly below (30 s) the iso electric line These findings are not in accordance with the present results the duration – amplitude relationship (Figs 1 & 3 and 2 & 4 respectively) was essentially the same whether the iso electric line or the trough served as reference level

As mentioned above and as seen in the paper by Skoog Welinder & Nilsson (1977) there are considerable inter individual differences in the magnitude of the off effects for which we so far have no definite explanation Clinical *c* wave recordings performed in our laboratory seem to indicate that untrained patients tolerate short (0 5 2 s) flashes better than longer ones On the other hand it may be more difficult to standardize the test with brief stimuli since the variable influence of off effects on the maximum *c* wave amplitude demonstrated in this paper must be taken into account The off effects cease to exert an influence upon the *c* wave peak at stimulus durations exceeding the

maximum implicit time (5 5 s) The use of flashes longer than about 5 5 s would eliminate the error created by the off effects provided that the stimulus intensity is the same as in the present study Of the shorter flashes the 1 s flash is preferred since this stimulus duration seems to give a reasonable *c* wave amplitude in combination with a minimal influence of off effects

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References

Alpern M & Faris J J (1956) Luminance Duration Relationship in the Electric Response of the Human Retina *J opt Soc Amer 46* 845–850

Brucke E T v & Garten S (1907) Zur vergleichenden Physiologie der Netzhautstrome *Pflugers Arch ges Physiol 120* 290–348

Burian H M (1970) The effect of variations of the stimulus rise time on the human electroretinogram A contribution to its temporal aspects *Invest Ophthal 9* 410–41

Einthoven W & Jolly W A (1908) The form and magnitude of the electrical response of the eye to stimulation by light at various intensities *Quart J exp Physiol 1* 373–416

Gotch F (1903) The time relations of the photo electric changes in the eyeball of the frog *J Physiol (Lond) 29* 388–410

Johnson E P & Bartlett N R (1956) Effect of Stimulus Duration on Electrical Responses of the Human Retina *J opt Soc Amer 46* 167–170

Jolly W A (1909) On the electrical response of the frog s eyeball to light *Quart J exp Physiol 2* 363–332

Knave B Nilsson S E G & Lunt T (1973) The human electroretinogram d. c. recordings at low and conventional stimulus intensities Description of a new method for clinical use *Acta ophthal (Kbh) 51* 716–726

Motokawa K & Mita T (1942) Über eine einfachere Untersuchungsmethode und Eigenschaften der Aktionsstrome der Netzhaut des Menschen. *Tohoku J exp Med 42* 114–133

Muller Limmroth H W (1953) Der Einfluss der Dauer des Reizlichtes auf das Elektroretinogramm *Pflugers Arch ges Physiol 257* 35–47

Niemeyer G (1973) Technical note Intracellular recording from the isolated perfused mammalian eye *Vision Res 13* 1613–1618

Niemeyer G (1975) The function of the retina in the perfused eye. *Docum ophthal (Den Haag) 39 1* 53–116

Noell W K (1953) Studies on the electrophysiology and the metabolism of the retina *U S Air Force SAM Project 21–1201–0004* Randolph Field Texas

Oakley B & Green D G (1976) Correlation of light induced changes in retinal extra cellular potassium concentration with *c* wave of the electroretinogram *J Neurophysiol* 39 5 1117–1133

Schmidt R & Steinberg R H (1971) Rod dependent intracellular responses to light recorded from the pigment epithelium of the cat retina *J Physiol (Lond)* 217 71–91

Steinberg R H Schmidt R & Brown K T (1970) Intracellular Responses to Light from Cat Pigment Epithelium Origin of the Electroretinogram *c* Wave *Nature (Lond)* 227 728–730

Skoog K O (1974) The *c* wave of the human d c registered ERG III Effects of ethyl alcohol on the *c* wave *Acta ophthal (Kbh)* 52 913–923

Skoog K O (1975) The directly recorded standing potential of the human eye *Acta ophthal (Kbh)* 53 120–132

Skoog K O & Nilsson S E G (1974a) The *c* wave of the human d c registered ERG I A quantitative study of the relationship between *c* wave amplitude and stimulus intensity *Acta ophthal (Kbh)* 52 759–773

Skoog K O & Nilsson S E G (1974b) The *c* wave of the human d c registered ERG II Cyclic variations of the *c* wave amplitude *Acta ophthal (Kbh)* 52 904–912

Skoog K O Welinder E & Nilsson S E G (1977) Off responses in the human d c registered electroretinogram *Vision Res* 17 409–415

Taumer R Rodhe N Wichmann W & Rover J (1976) Experiments Concerning the human C Wawe *Albrecht v Graefes Arch Ophthal* 198 139–153

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COMBINED STAINING OF CORNEAL ENDOTHELIUM BY ALIZARINE RED AND TRYPANE BLUE

BY

STEFFEN SPERLING

Combined staining by alizarine red and trypane blue is an easy and reliable method for *in vitro* visualization of corneal endothelial nuclei cellular borders and uncovered parts of the membrane of Descemet A stained full thickness wet mount can be prepared in less than five min The staining method and preliminary findings concerning endothelial morphology in the centre and in the periphery of normal corneas are presented

Key words corneal endothelium – trypane blue – alizarine red – cellular borders – donor cornea

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Steinberg R H Schmidt R & Brown K T (1970) Intracellular Responses to Light from Cat Pigment Epithelium Origin of the Electroretinogram c Wave *Nature (Lond)* 227 728–730

Skoog K O (1974) The c wave of the human d c registered ERG III Effects of ethyl alcohol on the c wave *Acta ophthal (Kbh) 52* 913–923

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A viable coherent sheet of endothelial cells is a prerequisite for the maintainance of a dehydrated cornea The morphology and the cohesion of corneal endothelial cells can be studied in flat preparations A thorough review on flat corneal preparations was published by Honegger & Schierholter (1963) Methods of staining and preparation have later been proposed by Oh (1963) (silver nitrate and Harris haematoxylin on a single layer preparation) Nicholas (1965) (Harris haematoxylin on whole mounts) Robbins et al (1965) (p nitro blue tetrazolium on whole mounts) and by Smolin (1968) (silver nitrate and celestine blue on a single layer preparation) The methods mentioned above are either difficult to handle time consuming or insufficient in relation to visualiza

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tion of nuclei and cellular borders When they work the combined staining and preparation techniques described by Oh (1963) and Smolin (1968) are outstanding Nuclei and cellular borders are clearly outlined in single layers of endothelial cells

This investigation was undertaken in order to develop an *in vitro* staining method suited for the visualization of endothelial cells in the periphery of fresh and cryopreserved corneas after the cutting of the central button for transplantation The demands on the method were stated as follows Cellular nuclei cellular borders and denuded parts of the membrane of Descemet should be clearly outlined Examination should be possible in an ordinary laboratory microscope fitted with an ordinary light source Preparation time should be short

Material and Methods

98 bovine eyes were enucleated immediately after exsanguination of the animals and transported to the laboratory within 30 min The corneas were removed from the globes bisected and stained The stained preparations were bisected once more and placed on a microscope slide with the endothelium upwards protected from evaporation by a cover glass and studied in an ordinary Zeiss laboratory microscope Photographic pictures were obtained with the same instrument fitted with a photo tubus Filter Yellow green Film Kodak Tri X

28 human eyes were obtained from bodies initially stored at 15–21°C for 6–9 h later at 4°C The corneas were excised with a scleral rim of 1 5 mm A central button with a diameter of 6 mm was punched out with a surgical trephine The button and the peripheral part was stained bisected mounted wet and studied as the preparations of bovine tissue Eight corneal buttons containing pathological cells were obtained immediately after excision in connection with keratoplasty and prepared in the same way as the normal central buttons

Results

A rapid method for visualization of endothelial nuclei was previously developed (99 % alkohol for 30 seconds trypane blue for 1 min Sperling 1974) In this study the primary emphasis was placed upon staining of cellular borders and denuded parts of the membrane of Descemet The staining properties of a number of dyes on unfixed bovine endothelium were investigated The results are summarized in Table I Alizarine red stains cellular borders in unfixed

Table I

Results obtained when staining of intercellular borders in unfixed bovine corneal endothelium was attempted

Dye	Staining time	No of preparations	Staining of cellular borders
Silver nitrate 0 25 % 0 5 % in dist. water pretreatment with sucrose 2 % u v light (2 4 8 16 min)	10 30 60 sec	30	variable staining artefacts
Alizarine red 2 % in 0 9 % NaCl	5 10 15 min	8	no selective staining
Alizarine red 2 % in tap water	2 4 8 min	8	variable staining artefacts
Alizarine red 1 % 2 % in dist water	2 4 8 min	6	intense staining artefacts
Alizarine saphirol 1 % in dist water	2 4 8 16 min	4	no selective staining
Haematoxylin a m Haidenhain (ironalum 2½ 10 %)	3/3 6/6 12/12 24/24 min	8	no selective staining
Nuclear fast red 2 g + 2 100 ml dist water	2 4 8 16 min	4	no selective staining
Naphtochrome green 0 5 % in dist water	2 4 8 16 min	4	no selective staining
Saturated ammonium purpurate in 0 1 n KCN	2 4 8 16 min	4	no selective staining
Ruthenium red 1 5 g/l in dist water	2 4 8 16 min	4	no selective staining
Alizarine red 2 % in dist water + dextrane 70 300 – 700 – 1100 mg/ml	[illegible] min	6	intense staining artefacts decreasing in proportion to dextrane concentration
Alizarine red 2 % in dist water + glucose 5 5 %	2 min	2	no selective staining
Alizarine red 2 % in deionized water + sucrose 1 026 – 2 736 – 4 104 g/ml	[illegible] min	16	intense staining reliable no artefacts

preparations only The dye is highly soluble in water and in many other liquids with even slight solubility in water Attempts to find a rapid method of fixation and dehydration by which the alizarine red staining of cellular borders could be retained in permanent flat mounts were unsuccessful

Final method

1 *Rinse the cornea briefly (seconds) in 0 9 % NaCl*

2 Stain for two min with 1 % alizarine red S (Alizarin Sulfonsaures Natrium) in deionized water to which 2 g of saccharose is added per 10 ml

3 Rinse briefly in 0 9 % NaCl

4 Immerse tissue in 99 % ethanol for 30 seconds

5 Immerse tissue in 0 25 % trypane blue in 0 9 % NaCl for 30–60 seconds

6 Rinse briefly in 0 9 % NaCl

7 Mount wet with cover glass on microscope slide

Brief treatment of the tissue with concentrated alcohol renders all cell walls permeable to trypane blue 0 25 % trypane blue selectively stain nuclei Inter cellular borders and denuded parts of the membrane of Descemet stain red nuclei stain blue The staining of nuclei and intercellular borders are illustrated in Figs 3 and 4 The staining of uncovered parts of the membrane of Descemet is illustrated by the photo of Henle s warts in the periphery of an otherwise normal cornea (Fig 1)

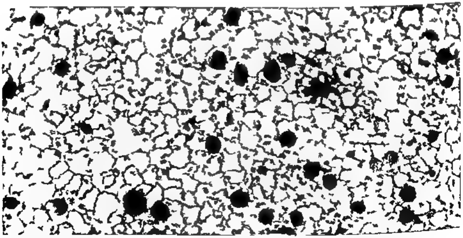

Fig 1

Henle s warts and multinuclear cells in the periphery of an otherwise normal cornea. Stained by alizarine red – trypane blue From a patient aged 81 years Primary magnification 10 x 8

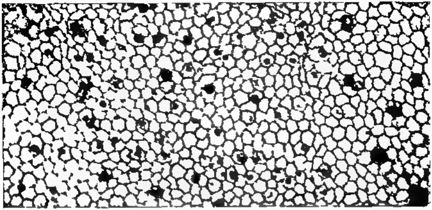

Fig 2

Artefacts obscuring endothelial leaks produced by a hypotonic solution of alizarine red. Central bovine cornea stained by 1 % alizarine red S in distilled water for two minutes Primary magnification 10 × 8

The method is equally suited for application on fresh bovine rabbit and human tissue and on cryopreserved human tissue In eight human eyes obtained 36 to 52 h post mortem cellular borders were sharply demarcated despite total obscurence of the endothelial pattern when investigated in specular reflex In two excised human corneas left in a moist chamber for seven days at 4° before staining the nuclei and the cellular borders stained well

Artefacts obscuring endothelial leaks are produced if rinsing is not performed if rinsing time is prolonged and if hypotonic solutions are used Artefacts produced by a hypotonic solution of alizarine red are shown in Fig 2 Cells appearing grey on the photograph are stained pink and the black dots are stained a heavy red colour The red dots mimic the staining of uncovered parts of the membrane of Descemet Sixteen human corneas in which an unbroken central endothelial sheet was observed by specular reflection was studied by the technique mentioned above In some corneas two patterns of cellular outline could be obtained On or close to the membrane of Descemet the intercellular borders appear sharply demarcated as wavy lines separating interdigitating cells At the surface of the cells the borders are not equally well outlined but they create a definite impression of linearity The picture at this level is one of mostly hexagonal cells well known from microscopy in reflected light Figs 3 and 4 are photographs of the same area In Fig 3 the microscope is focused on the base and Fig 4 on the surface of the cells

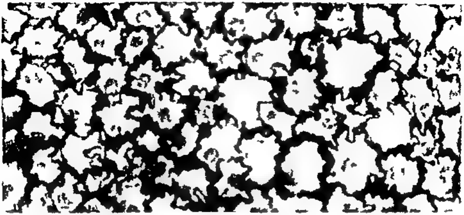

Fig 3

Endothelial cells in the centre of a normal cornea Microscope focused close to the membrane of Descemet Stained by alizarine red – trypane blue From a patient aged 90 years Primary magnification 30 × 8

The normal endothelial configuration seems to be related to the topographical position of the cells Centrally the cells are mononuclear and the nuclei appear circular or slightly oval Estimated nuclear size mean ± 50 % 60–80 % of the cells are hexagonal with areas mean ± 50 % Towards the periphery the cell size is more variable A peripheral zone of densely packed cells with oval nuclei is seen in some preparations At the extreme periphery the ratio of

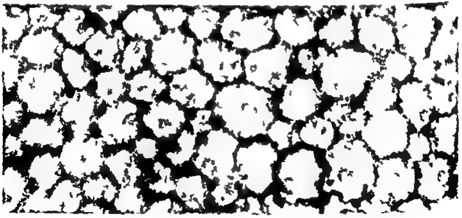

Fig 4

Endothelial cells in the centre of a normal cornea Photograph of the same cells as in Fig 3 Microscope focused on the surface of the cells facing the anterior chamber Stained by alizarine red – trypane blue Primary magnification 30 × 8

hexagonal cells decrease and large variations in cellular and nuclear size and shape are found Binuclear cells are common and budding and horseshoe formed nuclei appear The widths of these zones vary within each cornea and from one cornea to another

Eight corneal buttons removed from patients during keratoplasty were stained Multinucleated cells were common Deviations from the normal hexagonal cellular shape were marked and common Variations in the size of nuclei and in the size of mononuclear cells within the range of mean ± 500 % were seen Rodshaped clubshaped and budding nuclei were common

Comments

This method of staining and mounting is rapid and easy to handle It [redacted] reproducible provided that the alizarine red saccharose solution is not more than one month old Folding of the tissue interferes with exact focusing at high primary magnification The lack of permanent fixation restricts the use of the method to screening procedures Staining of intercellular borders by alizarine red in 0 9 % NaCl has been advocated by Vonwiller (1946) and by Stocker (1954) Repeated attempts at staining by this solution gave the same negative result

As cells with the same morphological characteristics as those in documented pathological corneas are not restricted to the extreme periphery of normal corneas it [redacted] not possible to draw conclusions regarding the central cellular morphology based on observations of an ill defined zone at the periphery More knowledge must be gained of normal variations of cellular morphology A quantitative study of cellular morphology in relation to topography is in progress

References

Honegger [redacted] & Schierholter [redacted] (1963) Das histologischer Bild des Hornhautendothels im Hautchenpraparat *von Graefes Arch f Ophth 166* 359–377

Nicholas J P (1965) Whole mounts of corneal endothelium *Arch Ophthal (Chicago) 73* 555–558

Oh J O (1963) Changes with age in the corneal endothelium of normal rabbits *Acta ophthal (Kbh) 41* 568–573

Robbins J E Capella J A & Kaufman [redacted] (1965) A study of endothelium in keratoplasty and corneal preservation *Arch Ophthal (Chicago) 73* 242–247

Smolin G (1968) A technique for staining and separating corneal endothelium *Amer J Ophthal* 65 9 232–236

Sperling S (1974) Corneal cryopreservation evaluated by Trypane blue staining *Ophthalm Res* 6 23–35
Stocker F W (1954) The endothelium of the cornea and its clinical implications *Trans amer ophthal Soc* 51 669–786
Vonwiller P C (1946) *Verhandl Schwei Naturforsch Gesellsch 1946* 194–195

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ATYPICAL RUBEOSIS IRIDIS IN CONGENITAL CYANOTIC HEART DISEASE

Report of a Case With Microhaemangiomas at the Pupillary Margin Causing Spontaneous Hyphaemas

BY

JENS CHRISTIAN KRARUP

Neovascularisation of the iris developed in a woman with congenital cyanotic heart disease This neovascularisation was predominately in the form of microhaemangiomas at the pupillary margin causing spontaneous hyphaemas Proliferative vascular alterations did not develop in the retina and secondary glaucoma did not occur

Key words congenital heart disease – microhaemangioma – neovascularisation – rubeosis iridis – spontaneous hyphaemas

Spontaneous hyphaemas in vascular anomalies and neovascularisation of the iris are not particularly frequent (Manor & Sachs 1972 Savir & Manor 1975) Such bleeding usually derives from pathological vessels as in classic rubeosis iridis or from microhaemangiomas at the pupillary margin Since Fechner (1958) reported the occurrence of spontaneous hyphaema from a microaneurism at the pupillary margin more reports have been published describing vascular anomalies localised at the pupillary margin Thus Cobb (1968) described 44

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Stocker F W (1954) The endothelium of the cornea and its clinical implications *Trans amer ophthal Soc* 51 669–786
Vonwiller P C (1946) *Verhandl Schweiz Naturforsch Gesellsch* 1946 194–195

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contorted vessels seemed embedded in a thinly yellow white stroma Moreover traces of blood were found between the trabulae of the iris in the right eye but no signs of bleeding were found in the left eye There were only a few newly formed vessels on the stroma of the irides and gonioscopy showed several dilated vessels in broad ciliary bands Ophthalmoscopy was found unaltered in relation to previous examinations Visual fields and tensions were normal During the next few years the patient had several recurrences of bleeding in the right anterior chamber all without preceding traumas In a few instances the bleeding could be directly observed from the haemangioma at the 11 o clock position in the right eye as a thin arched ray without pulsation down through the anterior chamber The first instance of spontaneous hyphaema in the left eye occurred in August 1974 After this there were several recurrences in both eyes Vision tension and visual field remained normal in both eyes Neo vascularisation did not develop in the retinae

Fig 1

Photograph of the right eye of a patient with congenital cyanotic heart disease showing part of the iris with microhaemangiomas at the pupillary margin at the 11 o clock position and a newly formed vessel with a tangential course (arrow) In the pupillary area a diffraction ring is seen around the angioma The vertical light streaks are reflexes from the cilia

Discussion

Rubeosis iridis originally designated as neovascularisation of the iris in diabetes mellitus has gradually come to cover any neovascularisation of the iris regardless of whether this be due to local or systemic causes (Ohrt 1967 Schulze 1967) Rubeosis iridis begins as extremely delicate vessels on the anterior surface of the iris close to the pupillary margin gradually forming a network within the iris frill Hereafter the vessels spread peripherally Aneurysmal expansions on the vessels are only exceptionally seen Ohrt 1967) The microhaemangiomas at the pupillary margin reported in recent years seem either to be chance findings at routine examinations or to be discovered because of the occurrence of spontaneous hyphaemas (Cobb 1968 Rosen & Lyons 1969 Sellman 1972 Israel & Lorenzetti 1974) Thus in these cases it cannot be excluded that these were congenital vascular anomalies rather than an atypical *rubeosis iridis* Cobb et al (1970) reported microhaemangiomas in 5 out of 10 patients with myotonic dystrophy and it is possible that there are other conditions where such microhaemangiomas frequently occur In the case described here the neovascularisation was predominately in the form of microhaemangiomas at the pupillary margins There were no proliferative vascular alterations in the retinae but on the contrary the well known picture of retinal cyanosis was observed (Richter & Richter 1965 Petersen & Rosenthal 1972) Rubeosis iridis can be a precursor of haemorrhagic glaucoma which however has not been reported as a complication of microhaemangiomas at the pupillary margin Glaucoma did not occur in the present case It is not known why some patients with neovascularisation of the iris or iris vascular anomalies develop spontaneous hyphaemas while others do not Neither is the cause of neovascularisation of the iris itself known However a prolonged stasis with subsequent hypoxia of the iris tissue is a common factor in those conditions where a local or systemic disease is known to be present (Ohrt 1967 Schulze 1967)

References

Cobb B (1968) Vascular tufts at the pupillary margin A preliminary report on 44 patients *Trans ophthal Soc U K* 88 211–221

Cobb B Shilling J S & Chisholm I H (1970) Vascular tufts at the pupillary margin in myotonic dystrophy *Amer J Ophthal* 69 573–582

Fechner P U (1958) Spontaneous hyphaema with abnormal iris vessels *Brit J Ophthal* 42 311–313

Israel M P & Lorenzetti D W C (1974) Bilateral microhemangiomas of the pupillary border with later hyphema *Canad J Ophthal* 9 138–140

Manor R S & Sachs W (1972) Spontaneous hyphema *Amer J Ophthal 74* 293–295
Ohrt V (1967) *Diabetic iridopathy* Universitetsforlaget i Århus
Petersen R A & Rosenthal A (1979) Retinopathy and papilledema in cyanotic congenital heart disease *Pediatrics 49* 243–249
Richter S & Richter K (1965) Augenhintergrundsveranderungen bei angeborenen Herzfehlern *Z Kreisl Forsch 54* 579–586
Rosen E & Lyons D (1969) Microhemangiomas at the pupillary border *Amer J Ophthal 67* 846–853
Savir H & Manor R S (1975) Spontaneous hyphema and vessel anomaly *Arch Ophthal (Chicago) 93* 1056–1058
Schulze R R (1967) Rubeosis iridis *Amer J Ophthal 63* 487–495
Sellman A (1972) Hyphaema from microhaemangiomas *Acta ophthal (Kbh) 50* 58–61

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THE INFLUENCE OF THE NICTITATING MEMBRANE ON STEROID INHIBITION OF LIMBAL WOUND HEALING

BY

DAVID MILLER and PATRICIA O CONNOR

In a study involving 84 rabbits it was found that local corticosteroids inhibit limbal wound healing in normal rabbit eyes and do not inhibit similar wounds if the nictitating membrane has been removed It was further found that the contact time of fluorescein labelled corticosteroids is almost 3 times longer in rabbit eyes with nictitating membranes than those in which the membranes have been removed

Key words corticosteroid – limbal wound – nictitating membrane – contact time wound healing

The inhibiting effect of topically applied corticosteroids on wound healing is well documented (Aquavella Gasset & Dohlman 1964 Palmerton 1965 Sugar & Chandler 1974 Fink & Baras 1956 McDonald Borgmann Roberts & Fox 1970 Hanna Fraunfelder Cable & Hardberger 1973)

In our previous studies involving the effect of soft contact lenses on wound healing (Miller & Marchevsky 1976) the nictitating membranes were amputated to facilitate retention of the soft lens At the start of the present experiment this practice was continued to facilitate wound observation

It soon became apparent that the nictitating membrane did have a definite and measurable effect on the influence of steroids on wound healing This paper quantitated that effect and proposes plausible explanations for this phenomenon

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Method

A group of 34 albino rabbits (17 male 17 female) were used in experiment 1 Each rabbit was anaesthetized with 30 mg/kg of Sodium Pentobarbital (Diabutol) given intravenously The rabbits were divided into 2 groups with an equal sex distribution In one group immediately prior to the limbal surgery the nictitating membranes were removed from each eye The other group retained the nictitating membranes Under microscopic observation and using a lid speculum each eye of each rabbit in each group received a 12 mm limbal incision superiorly The limbal wound was then closed with a continuous 9–0 nylon (ethilon) suture with an anchoring knot at either end of the wound Since the rate of healing might vary depending on the tightness of the suture one researcher performed all the operations Immediately after the operation a drop of Polymyxin B Neomycin Gramicidin (Ophthalmic Neosporin) was instilled in each eye

For the next ten consecutive days one drop of a commercial preparation of 0 1 % dexamethasone sodium phosphate (Decadron) solution was placed in the right eye of every animal three times a day A vehicle control was placed in the left eye of each animal three times a day One drop of Polymyxin B Neomycin Gramicidin (Neosporin ophthalmic solution) was used in each eye twice a day This is a routine clinical procedure used to prevent postoperative infection

Measurement of wound strength took place on the 10th postoperative day The animal was sacrificed with an overdose of iv barbiturate anaesthesia The wound sutures were then removed from the eyes The eyes were cannulated with a 25 gauge needle The needle was attached in parallel via tubing to both a manomter and a pressure application system The pressure system in this case was a water faucet The faucet was controlled so that the column of mercury rose at a constant rate of 20 mmHg/second One observer then controlled the pressure increase and watched the manometer while the other observer watched the wound through a 10 x operating microscope Bursting pressure was recorded when the wound was first noted to gape

After evaluating the results a second experiment was performed in which 1/30 ml of fluorescein dexamethasone combination was instilled both into a virgin eye and into the other eye of the same animal in which the nictitating membrane had been removed the day before the test

This solution was freshly prepared by combining 0 02 g of a commercial sodium fluorescein in solution with 2 5 ml of a commercial preparation of 0 1 % dexamethasone phosphate ophthalmic solution producing a concentration of 0 016 % sodium fluorescein

Exactly 1/30 ml of the fluoresceinated dexamethasone was instilled in each eye of the rabbit The animal s lids were then manually blinked to disperse the solution evenly on the corneal surface A cobalt blue filter was placed over a fibrioptic light source and held by one observer at a distance of one foot from the animal s eye Another observer timed the disappearance of the fluoresceinated dexamethasone from the lower tear meniscus Four trials were conducted on each eye and the disappearance time of the solution recorded

Results

Results of experiment 1 are recorded in Table I Statistically we evaluated our results using the paired *t* test The data from group I rabbits (nictitating membranes removed) demonstrated that dexamethasone had no significant effect on corneal wound strength after the nictitating membrane had been amputed In group II rabbits (nictitating membrane intact) the wound strengths of the steroid treated eyes were diminished by 16 % which was significantly less than those of the control group ($P < 0\ 05$)

The results of the second experiment are recorded in Table II This data clearly demonstrates that the contact time of the fluoresceinated dexametha sone was almost 3 times longer in the normal eye than in the eye without a nictitating membrane

Table I
Effect of topically applied dexamethasone on corneal wound strength

	No of eyes	Wound tensile strength (± SD) (mmHg/12 mm wound)	Significance level difference between means using paired *t* test
Dexamethasone nictitating membrane removed – 10 days post op			
Treated eye	16	961 25 ± 220 05	$P > 0\ 10$
Contralateral eye	16	811 25 ± 240 31	
Dexamethasone nictitating membrane intact – 10 days post op			
Treated eye	18	685 78 ± 229 33	$P < 0\ 05$
Contralateral eye	18	804 44 ± 300 63	

Table II
Disappearance time of fluorescent dexamethasone

Group	No of trials	Mean (± SD) contact time (min)
Fluorescent dexamethasone nictitating membrane removed	4	3 2 ± 0.5
Fluorescent dexamethasone nictitating membrane intact	4	8 0 ± 0 67

Discussion

It is apparent from the above data that the nictitating membrane modifies the corticosteroid effect on wound healing It is not clear however whether the reason is mechanical or biochemical A major clue to this puzzle arose from the finding that sodium fluorescein added to the dexamethasone solution has a contact time measured visually which is almost three times longer in the normal eye than in the eye without the nictitating membrane Although we do not know if the fluorescein actually combines with the dexamethasone, we suspect that if fluorescein is present then dexamethasone must also be present.

Certain details of the rabbit s anatomy may explain the finding Secretions from the lacrimal gland the nictitans gland and the Harderian gland constitutes the rabbit tears The nictitans and the Harderian secretions contain mucous and oil Both of these glands which are located in the orbit empty into the nictitating membrane (Prince 1964) Thus the removal of the membrane effectively shuts off the contribution of these glands to the tears Just as in the case of viscous vehicles used with topical ophthalmic medications (Benedetto Shah & Kaufman 1975) the viscous secretion of these glands tend to retain the rabbit tears and any medication added to the tears The above logic may explain the results of the experiment

Another possibility remains Medication contact time could be shortened if the removal of the nictitating membrane induced an irritation which increased the flow from the lacrimal gland tending to wash out the medication Therefore the Schirmer strip test was performed on an animal one of whose eyes had the membrane removed The results showed the lacrimal secretion to be of the same amount in each eye

Thus the explanation of the results may be that the secretions of the nictitans and Harderian glands increase the tear plus steroid contact time on the ocular surface If the nictitating membrane is removed the secretions of these glands are effectively turned off and the steroid has less contact time with the wound

The study further illustrates the point that information gained from rabbit eye experiments concerning drug effects and lacrimal dynamics cannot simply be transferred to the human eye

References

Aquavella J V Gasset A R & Dohlman C H (1964) Corticosteroids in wound healing *Amer J Ophthal* 58 621–626

Benedetto D A Shah D O & Kaufman H E (1975) The instilled fluid dynamics and surface chemistry of polymers in the preocular tear film *Invest Ophthal* 14 887–902

Fink A I & Baras I (1956) Effect of steroids on tensile strength of corneal wounds *Amer J Ophthal* 42 759–764

Hanna C Fraunfelder F T Cable M & Hardberger R E (1973) The effect of ophthalmic ointments on corneal wound healing *Amer J Ophthal* 76 193–200

McDonald T O Borgmann A R Roberts M D & Fox L G (1970) Corneal Wound Healing I Inhibition of stromal healing by three dexamethasone derivatives *Invest Ophthal* 9 703–709

Miller D & Marchevsky A (1976) Effect of soft contact lenses on limbal wound healing *Exp Eye Res* (in press)

Palmerton E S (1955) The effects of local cortisone on wound healing in rabbit corneas *Amer J Ophthal* 40 344–352

Prince J H (19 0) *The Rabbit in Eye Research* pp 33–56 79-[illegible] Charles C Thomas Publishing Co Springfield

Sugar J & Chandler J W (1974) Experimental corneal wound strength *Arch Ophthal (Chicago)* 92 248–249

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REINFORCED EPISCLERAL CERCLAGE IN RETINAL DETACHMENT

A Note on Surgical Technique

BY

PEEP ALGVERE

Episcleral silicone rods are used as encircling elements in retinal detachment surgery In order to reinforce the encircling effect and form a stable effective buckle the episcleral silicone rod is combined with an Arruga suture or a fairly rigid teflon band The Arruga string (a 9-0 supramid suture) is sewn in a longitudinal direction into a solid silicone rod (2 mm in diameter) or into a silicone half cylinder (diameter 3 or 4 mm) Soft sponge like rods can also be reinforced with a 2 mm broad teflon band placed on the flat surface of the half cylindrical silicone element Drainage of subretinal fluid is usually performed in order to make room for the high circumferential buckle
Experience has shown that this modified encircling procedure is very useful in complicated cases of retinal detachment

Key words reinforced cerclage – episcleral silicone rod – Arruga suture – teflon band – retinal detachment

Schepens et al (1957) introduced the encircling procedure for retinal detachment surgery using an intrascleral polyethylene tube for scleral buckling (following a scleral resection) A few years later the combination of a flat silicone band with various silicone implants was developed (Regan et al 1962) Arruga (1958) described the use of an encircling suture placed on the sclera around the equator

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of the eye The Arruga suture although simple and easy to use often fails to seal retinal breaks It may even cut through the sclera and choroid and cause the "string syndrome

Since the publication of Custodis work (1951) it has become evident that intrascleral implants in most cases can be replaced by episcleral elements Girard & McPherson (1962) used circumferential silicone rubber rodding on full thickness sclera Encircling episcleral silicone rods or sponges fulfill the requirement of a broad indentation area around the whole circumference of the globe However they are sometimes difficult to anchor in the sclera particularly if the sclera is thin or oedematous after previous surgery The silicone elements may after some period of time loosen or even extrude through the conjunctiva In order to reinforce the encircling effect and form a stable effective buckle we have found it very useful to combine the encircling silicone rod procedure with an Arruga suture

Procedure

When a high encircling buckle is required a silicone rubber rod (diameter 2 3 or 4 mm) is used Silicone rods are available in different qualities and elasticities We use a solid but not inelastic compact cylinder (Trelleborgs Gummifabrik Trelleborg Sweden) or a soft spongelike rod (Klein Heidelberg Germany) The Arruga string is an encircling 2–0 supramid suture (Astra, Sodertalje Sweden) As an alternative to this encircling supramid suture sponge like rods (preferably those 4 mm in diameter) can be easily reinforced with a 2 mm broad teflon band of a fairly rigid quality (Husman St Gallen Switzerland)

When using the 2 mm rod the encircling supramid suture is sewn into the silicone rod in a longitudinal direction most of the suture being buried inside the rod When working with a thicker rod (3 or 4 mm diameter) it is cut to a half cylinder in order to reduce the resulting bulge outside the eye s curvature The half cylinder is applied with its curved surface against the sclera and pressed in so that the flat surface is in line with the eye s curvature The encircling supramid suture is threaded in broad stitches through the superficial part of the rod s flat side (Fig 1) The silicone rod is placed over the greatest circle of the globe and anchored to the sclera with mattress like sutures (Polytek 5–0 SSC Neuhausen Switzerland) in each quadrant of the eye (Fig 2)

As a rule drainage of subretinal fluid through a sclerotomy (2–3 mm long) is necessary in order to create enough space for a high circumferential buckle made of the solid type of rod If no subretinal fluid is released the intraocular

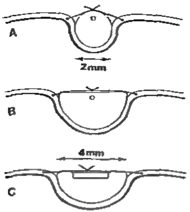

Fig 1

Encircling episcleral silicone elements shown in schematic cross section

A The 2 mm rod can form a buckle of desired height according to the tightening of sutures Encircling supramid suture (Arruga suture) is seen as small circle inside rod

B Half cylinder of 4 mm solid silicone rod with Arruga suture (small circle inside rod) produces a buckle the circular curvature of which indents about 6 mm of sclera in antero posterior direction of the eye

C Soft sponge like rod (4 mm diameter) cut to half cylinder reinforced with teflon band provides a broad buckle that is lower than that of solid silicone (B)

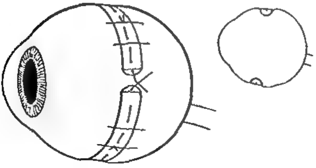

Fig 2

Half cylinder of solid silicone rod reinforced with Arruga suture is placed episclerally around greatest circumference of eye.

Fig 3
Fundus photograph (45° view) of circumferential buckle (to the right on picture) formed by an episclerally placed 2 mm solid silicone rod reinforced with Arruga suture Myopic eye (–20 D) of 35 year old male 6 months after surgery

pressure usually becomes too high blocking retinal circulation and causing haze of the ocular media When the soft sponge like rod is used drainage can sometimes be avoided (cf Lincoff et al 1975)

The Arruga suture is then stretched and tied so that the both ends of the rod meet at the knot Additional Polytek sutures may be placed into sclera wherever a deeper indentation is deemed necessary In this way a high and broad buckle is produced around the whole circumference of the eye (Fig 3)

Discussion

Encircling procedures have proven valuable in surgery of complicated cases of retinal detachment such as seen in aphakia and high axial myopia In the majority of such cases the detached retina does not flatten on immobilization of the eye with traction sutures an observation indicating considerable vitreous traction (Algvere & Rosengren 1977) Encircling buckles are useful in several

other conditions for example when retinal breaks are present in more than one quadrant of the eye In cases with large retinal tears even rigid narrow bands alone (e g 2 mm teflon band) are usually insufficient and broader buckles that make a deep indentation are required to close these breaks

Generally it is much easier and less dangerous to use episcleral silicone elements than intrascleral implants However in certain situations it may be difficult to affix an encircling episcleral silicone rod or sponge permanently in a proper position The reinforcement with the supramid suture (or teflon band) secures the encircling rod in an appropriate position which can be expected to be stable over a long period of time even though the sutures anchoring the rod to sclera may loosen after some time

In several encircling techniques an elastic silicone rod or band is stretched around the eye reduced to desired length and tied in that shortened position According to Lincoff et al (1975) the band as it contracts drives fluid from the eye and provides space for its own intrusion The height of the buckle will then be influenced by several factors some of which are obvious the elastic properties of the silicone material the width of the encircling element the intraocular pressure and the rigidity of the eye The importance of a controlled encircling method producing an indentation of known height was advocated in order to avoid complications related to the tightness of the encircling band (Hamilton & Taylor 1972) Lincoff et al (1976) have called attention to the deformation of the ocular shape (reduction of equatorial diameter elongation of axial length) caused by a cerclage When using elastic sponge like rods the buckles produced were measured to be flatter than calculated These authors assumed this difference to be due to the change in ocular shape

The present method (silicone rod and encircling supramid suture) provides a buckle of known height which can be predetermined For example a solid half cylinder of a 4 mm rod placed with its flat surface in line with the eye s curvature will produce a scleral indentation of almost 2 mm This height is not influenced by ocular pressure or rigidity since the solid silicone material is barely compressed The encircling supramid suture stabilizes the outer edge of the silicone element in its place for a very long time

A soft sponge like rod procedures a flatter buckle since this silicone material will be compressed under the encircling supramid suture or teflon band In this case the degree of compression may vary due to the ocular pressure and rigidity Nevertheless the indentation of sclera can never exceed the original thickness of the silicone element as long as the reinforcing suture or band are in line with the eye s curvature

The stabilization of the cerclage is crucial for the operative result Complicated cases of retinal detachment are often associated with considerable

vitreous shrinkage and traction or massive preretinal proliferation The encircling buckle decreases the equatorial diameter of the vitreous space and thus relieving some traction If the buckle flattens – the vitreous traction still being present – the retinal tear may re open and consequent detachment is likely to occur In addition the reduction of vitreous traction on the retina probably has a prophylactic effect on the formation of new tears and redetachment (for full discussion see Urrets Zavalia 1968)

References

Algvere P & Rosengren [illegible] *(1977) Immobilization of the eye – evaluation of a new* method in retinal detachment surgery *Acta ophthal (Kbh) 55 803*

Arruga H (1958) Le cerclage equatorial pour traiter le décollement retinien *Bull et Mem Soc Franç Ophthal 71 571*

Custodis E (1951) Beobachtungen bei der diathermischen Behandlung der Netzhautablosung und ein Hinweis zur Therapie der Amotio retinae *Ber dtsch ophthal Ges 57 227*

Girard L J & McPherson A R (1962) Scleral buckling full thickness and circumferential using silicone rubber rodding and photocoagulation *A M A Arch Ophthal 67* 409

Hamilton A M & Taylor W (1972) Controlled encircling procedure for retinal detachment *Brit J Ophthal 56* 695

Lincoff H Ramirez V Kreissig I Baronberg N & Kaufman D H (1975) Encircling operations without drainage of subretinal fluid *Mod Probl Ophthal Vol 15* 188 Karger Basel

Lincoff H Kreissig I & Parver L (1976) Limits of constriction in the treatment of retinal detachment *A M A Arch Ophthal 94* 1473

Regan C D J Schepens C L Okamura I D Brockhurst R J & McMeel J W (1969) The scleral buckling procedures VI Further notes on silicone in primary operations *A M A Arch Ophthal 68* 313

Schepens C L Okamura I D & Brockhurst R J (1957) The scleral buckling procedures I Surgical techniques and management *A M A Arch Ophthal 58 797*

Urrets Zavalia A (1968) *Le decollement de la retine* [illegible] 52° Masson & Cie Paris

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IN VITRO INVESTIGATIONS ON THE EFFECT OF PILOCARPINE ON THE METABOLISM IN PIG LENSES ILLUSTRATED WITH SOME INTERMEDIATE METABOLITES

BY

ANNE KLAUBER

[illegible] pairs of pig lenses were incubated in TCM 199 o g with pilocarpine 5×10^{-4} M and 10^{-2} M 5×10^{-4} M = the probable concentration in the aqueous during ordinary pilocarpine medication
The concentration of l lactate, pyruvate RTP RDP and AMP was determined in the lenses and the assimilation of glucose and the produc tion of l lactate and pyruvate were measured
As far as pilocarpine 5×10^{-4} M was concerned no significant differences were found but pilocarpine 10^{-2} M gave a significantly higher l lactate concentration in the lenses (118 %) and increased the assimilation of glu cose to 120 % and also augmented the production of l lactate to 168 % and the pyruvate to 134 % tending to show that pilocarpine 10^{-2} M in creased the glycolytic activity in the lenses The concentrations of RTP RDP and AMP were unchanged

Key words pilocarpine – lens crystalline – cataract – *in vitro* – glycolyse – glucose – l lactate – ribonucleotide

Over the last 20 years there has been an intensive clinical and experimental investigation into the cataractogenic effect of miotics

In 1966 Axelsson & Holmberg examined the occurrence of lens opacities in patients who were treated for more than six months with pilocarpine or echo thiophate (phospholinodid®) 10 % of 103 eyes showed incipient or increased lens opacities after treatment with pilocarpine and 50 % of 48 eyes treated with echothiophate respectively The occurrence of lens opacities was inde pendent of whether the lens was clear or opaque before treatment began

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Abraham & Teller (1969) concluded from a prospective investigation that pilocarpine and echothiophate might be used on patients under 65 years of age without fear of lens opacities but in older patients the strongest miotics seemed to produce a greater percentage of lens opacities and in a shorter time Hockwin et al (1966) showed that pilocarpine had an accellerating effect upon experimental naphthalene cataracts in rabbits They used biomicroscopic investigations of the lenses

Muller et al (1956) discovered that pilocarpine 10^{-3} M inhibited the oxygen absorption in pig lenses *in vitro* and an increase of the pilocarpine concentration to 4×10^{-3} M stopped the oxygen consumption completely The concentration of pilocarpine that totally inhibited the oxygen assimilation for a human lens *in vitro* was 10^{-3} M

After incubation with pilocarpine Mayer (1976) found that the oxygen consumption of cultured lens epithelial cells was lowered by 70 % to 30 % of the normal value The glucose consumption did not change significantly The pilocarpine concentration used was 2.5×10^{-5} M

Michon & Kinoshita (1968) demonstrated that pilocarpine did not cause macroscopical changes in rabbit lenses but did cause microscopic epithelial cell changes and a slight increase in the water content (2 2 mg per lens) without changing the sodium and potassium concentrations

Muller et al (1960) found a concentration of pilocarpine of about 10^{-} M (215 μg/0 1 ml) in human humour aqueous after local application of 2 drops of 2 % pilocarpine In 1964 the same investigators (Hockwin et al) found a concentration in rabbits aqueous of 5×10^{-3} M after 3 drops of 1 % pilocarpine had been used They used polarographic determinations of pilocarine The resorption percentage was between 20 % and 11 %

On the other hand Asseff et al (1975) only found a concentration in the aqueous of 6×10^{-4} M (12 μg/0 1 ml) in monkeys five min after 100 μl 4 % pilocarpine had been applied After about 10 min the concentration had decreased to 5×10^{-4} M The resorption percentage was about 2 They used radioactive determination with labelled pilocarpine

The purpose of this present work is to investigate the influence of pilocarpine upon the metabolism in normal pig lenses by *in vitro* experiments

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Abbreviations

RTP ribonucleoside triphosphate
RDP ribonucleoside diphosphate
AMP adenosine 5 monophosphate
ATP adenosine 5 triphosphate
ADP adenosine 5 diphosphate
TCM 199 Tissue Culture Medium 199 (Difco)

Materials and Methods

Fresh lens pairs from 22 slaughterhouse pigs (Danish Landrace) (6–8 months old) were prepared via an anterior approach. The lenses were incubated in 25 ml closed test tubes in 5 g Difco Tissue Culture Medium 199. The lenses were placed with the reverse side down and the liquid layer over the lens was less than 2 cm. The medium contained glucose, amino acids, vitamins and electrolytes. To prevent bacterial contamination Na penicillin 500 IE/ml and streptomycin 0.5 mg/ml were added. The incubation temperature was 37°C and pH 7.4–7.6. Pilocarpine hydrochloride 4% was added making concentrations of 5×10^{-4} M or 10^{-} M. The change in pH was corrigated with sodium bicarbonate.

After 22 h incubation the lenses were inspected macroscopically for possible opacities, frozen in liquid nitrogen and stored at –20°C until analyses could be carried out. The lenses were weighed in the medium before incubation and directly on the scales after incubation. The medium was weighed before incubation.

The lenses were treated in accordance with the methods used by Laursen (1976) and the biochemical analyses of l lactate, pyruvate, RTP, RDP and AMP were carried out as described in Bergmeyer (1974) with modifications as described by Laursen (1976).

Every statement of concentrations is expressed per kg wet lens weight.

The amount of glucose used was calculated from the fall in concentration in the incubation medium, and the production of l lactate and pyruvate was calculated from the concentrations in the medium after incubation.

The percentage of the glucose which was converted into l lactate was calculated according to the formula $\dfrac{\text{l lactate production}}{\text{glucose used} \times 2} \times 100\,\%$

The statistical analyses were Willcoxon rank sum test for pair differences (Therkelsen 1968). The level of significance was 95%.

Results

After incubation with 5×10^{-4} M pilocarpine every lens was transparent and unchanged in weight. There were no significant differences in the concentrations of RTP, RDP, AMP, l lactate and pyruvate between treated and control lenses. The glucose used and production of l lactate and pyruvate was also without significant differences (see Table I).

After incubation with pilocarpine 10^{-} M all treated lenses became superficially diffusely opaque, partly on the anterior side, partly on the posterior side where the points of contact with the inside of the test tube were very marked. No profound opacities could be detected.

The concentrations of RTP, RDP and AMP in the lenses lacked significant differences inasmuch as the concentration of RTP was 2272 μmol/kg against 2162 μmol/kg in control lenses ($P > 0.05$), RDP concentration was 616 μmol/kg against 594 μmol/kg in control lenses ($P > 0.05$) and the concentration of AMP

39*

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Abbreviations

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RDP ribonucleoside diphosphate
AMP adenosine 5 monophosphate
ATP adenosine 5 triphosphate
ADP adenosine 5 diphosphate
TCM 199 Tissue Culture Medium 199 (Difco)

Table II

The concentrations of intermediate metabolites in pig lenses after incubation for 22 h in TCM 199 containing 10- M pilocarpine And the control lenses Median 25 and 75 percentiles in brackets and P values

N = 12	Pilocarpine 10- M		Control lenses		P
l lactate mmol/kg	8.5	(7.8–9.2)	7.2	(6.8–7.5)	< 0.01
Pyruvate μmol/kg	59	(?7–78)	[illegible]	(39–103)	> 0.05
RTP μmol/kg	2272	(2186–2451)	2162	(2133–2347)	> 0.05
RDP μmol/kg	616	(587–641)	594	(562–690)	> 0.05
AMP μmol/kg	205	(196–266)	178	(149–271)	> 0.05
Glucose uptake mmol/kg/22 h	22.4	(19.4–26.0)	18.6	(16.8–21.0)	< 0.01
l lactate production mmol/kg/22 h	43.9	(40.0–46.5)	26.1	(24.6–26.7)	< 0.01
Pyruvate production μmol/kg/22 h	2 8	(234–315)	151	(139–164)	< 0.01
% glucose converted to l lactate	99	(91–105)	72	(61–78)	< 0.01
Weight mg	435	(405–446)	431	(407–457)	> 0.05
Loss in weight mg/lens	9	(4–10)	5	(2–7)	> 0.05

verted into l lactate by the glycolytic process was significantly higher in the lenses which were incubated in 10- M pilocarpine the per cent being 99 against 72 in the control lenses The loss in weight lacked significant differences – 9 mg/lens in treated lenses and 5 mg/lens in control lenses ($P > 0.05$)

Discussion

The concentrations of pilocarpine of 5×10^{-4} M and 10 M used in the present investigation were chosen because 5×10^{-4} M is the probable concentration in the aqueous during ordinary medication with pilocarpine (Asseff et al 1973) and 10- M is certainly so high that oxygen consumption in the lenses is re strained (Muller et al 1956)

In the present investigations no significant changes were discovered in the

concentrations of RTP RDP or AMP in the lenses which were incubated even with the highest pilocarpine concentration

Hockwin et al (1966) found that bovine lenses incubated together with pilocarpine 10^{-3} M decreased the ATP concentration to 78 % and raised the ADP and AMP concentration to 168 % and 132 %

As one of the effects of pilocarpine is to create anaerobic conditions for the lens (Muller et al 1956) it might be permissible to compare the results obtained with those obtained under anaerobic incubations

Kinoshita et al (1961) found that calf lenses incubated anaerobically maintained their high energy phosphate level if the incubation medium contained glucose

Conversely van Heyningen & Linklater (1975) found that the concentration of ATP was decreased to 65 % in bovine lenses incubated under anaerobic conditions So did Radetzkv (1971) who found a lowered ATP and an increased AMP in bovine lenses incubated with KCN 10^{-5} M

The l lactate concentration in the lens in the present investigation was significantly higher in the lenses incubated with 10- M pilocarpine and the measured production of l lactate increased to 168 % The increase in the pyruvate production was 184 % and the corresponding increase in the glucose absorption was 120 % In freshly prepared lenses the l lactate concentration is 8 5 mmol/kg (N = 38) (own results unpublished) This shows that the change in the l lactate concentration in the lens is not sufficient to affect the l lactate production result

Under anaerobic conditions van Heyningen & Linklater (1975) found an increase in the lactate production to 165 % for bovine lenses and van Heyningen (1965) found an increase in glucose consumption to 130 % in lenses from adult rabbits under anaerobic conditions

This means that the increase in production of l lactate and the increase in glucose used under anaerobic conditions corresponds to the results found in the present work The results found indicate that an increased glycolytic activity takes place when the lenses are incubated in pilocarpine 10- M

Glucose 6 phosphate dehydrogenase in rabbit lens homogenate is inhibited about 50 % by pilocarpine 4×10^{-5} M in the course of 22 h but when a whole lens is used the necessary concentration is 0 2 M (Carenini & Orzalesi 1966) Pilocarpine (0 2 M and 0 1 M) has an inhibiting effect upon rabbit muscle lactate dehydrogenase together with inactivating SH groups (Fiore & Delogu 1969) The concentration necessary to inhibit the lactate-dehydrogenase by almost 50 % is 10 times higher than the highest concentration used in the present work On account of this only moderate inhibition might be expected here

By *in vitro* experiments with rat lenses Sippel (1962) calculated that respiration accounts for less than 33 % of the energy derived from glucose catabolism So if pilocarpine (10 M) inhibits the oxygen consumption completely an increase in l lactate production by 168 % should be sufficient to supply the deficit in RTP production

The reason why some workers (Hockwin et al 1966 Radetzky 1971 van Heyningen & Linklater 1975) find a deficit in the energy rich nucleotides concentration whereas others (Kinoshita et al 1961 and the present work) do not is probably that the first mentioned group operates with old lenses and the last group with young lenses with a relatively lower weight

Conclusion

The present work has shown that pilocarpine 10 M affects pig lenses *in vitro* so that the lenses become superficially diffusely opaque have a stable level of energy rich ribonucleotides and have an increased glycolytic activity whilst the production of l lactate and pyruvate is increased

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References

Abraham S V & Teller J J (1969) Influence of various miotics on cataract formation *Brit J Ophthal 53* 833-838

Asseff C F Weisman R I Podos S M Becker B (1973) Ocular penetration of pilocarpine in primates *Amer J Ophthal 75* 212-215

Axelsson U & Holmberg Å (1966) The frequency of cataract after miotic therapy *Acta ophthal (Kbh) 44* 421-429

Bergmeyer H U (1974) *Methoden der Enzymatischen Analysen Vol II* Verlag Chemie, Weinheim

Carenini B B & Orzalesi N (1966) Richerche sperimentale sull azione catarattogena di alcuni colliri miotici *Boll Ocul 45* 847-861

Fiore G & Delogu A (1969) Meccanismo di azione della pilocarpina sulla lattico deidrogenasi *Ann Ottal clin Oculist 95* 569-572

Hockwin O Muller H K Blaser U (1964) Nachweis von Pilocarpin im Kammerwasser von Kaninchenaugen mit Hilfe der Polarographie *Albrecht v Graefes Arch Ophthal 167* 459-466

Hockwin O Okamoto T Licht W Noll E (1966) Effect of Pilocarpine on Lens Metabolism *Ophthalmologica 152* 46–56

Kinoshita J H Kern H L Merola L O (1961) Factors affecting the cation transport of calf lens *Biochim biophys Acta 47* 458–466

Laursen A B (1976) Concentrations of some ribonucleotides L-lactate and pyruvate in human senile cataractous lenses with special reference to anterior capsular/subcapsular opacity *Acta ophthal (Kbh) 54* 677–692

Mayer U (1976) Wirkung des Pilocarpins auf den Stoffwechsel von uberlebenden Linsenepithelium und Irisgewebe *Klin Mbl Augenheilk 168* 531–537

Michon J & Kinoshita J H (1968) Experimental miotic cataract *Arch Ophthal (Chicago) 79* 79–86

Muller H K Kleifeld O Hockwin O Dardenne U (1956) Der Einfluss von Pilocarpin und Mintacol auf den Stoffwechsel der Linse *Ber dtsch ophthal Ges 60* 115–120

Muller H K Hockwin O Kleifeld O (1960) Die Bestimmung von Pilocarpin im menschlichen Kammerwasser mit Hilfe der Polarographie *Albrecht v Graefes Arch Ophthal 162* 107–110

Radetzky W (1971) *Untersuchungen des Kohlenhydratstoffwechsels von Linsen nach Aufbewarung in Nahrlosungen mit Unterschiedlichem* O *Partialdruck* Rheinische Friedrich Wilhelms Universitat Bonn

Sippel T O (1962) The relationship of rat lens respiration to oxygen concentration and pH *Invest Ophthal 1* 385–389

Therkelsen A J (1968) *Medicinsk statistik* p 139 Akademisk Boghandel Århus

van Heyningen R (1965) The metabolism of glucose by the rabbit lens in the presence and absence of oxygen *Biochem J 96* 419–431

van Heyningen R & Linklater J (1975) The metabolism of bovine lens in air and nitrogen *Exp Eye Res 20* 393–396

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THE VALUE OF FLUORESCEIN FUNDUS ANGIOGRAPHY IN EVALUATING OPTIC DISC OEDEMA

BY

NILS ANMARKRUD

43 patients with blurred disc margins were studied by means of fluorescein fundus angiography The differentiation between very early disc oedema and a normal disc was possible due to an increased capillary network some microaneurysms and the late fluorescence located in a special circular manner at disc margin It was not possible to differentiate between optic neuritis and papilloedema although minor differences may exist Ischaemic optic neuropathy is a type of optic disc oedema which clearly differs from other causes of oedema when studied by fluorescein fundus angiography The method is especially suitable in differentiating pseudopapilloedema from genuine oedema of the optic disc

Key words fluorescein fundus angiography – optic disc oedema – drusen of the optic disc – ischaemic optic neuropathy – pseudotumour cerebri

An optic disc with blurred margins is a common finding in both ophthalmological and neurological practice The differentiation between oedema of the optic disc and pseudopapilloedema is important because oedema of the optic disc may be the first sign of a serious intracranial disease On the other hand the diagnosis of pseudopapilloedema can save the patient from unpleasant examinations which may even involve risks of complications

Shortly after Novotny & Alvis (1960 1961) described fluorescein fundus angiography Miller et al (1965) demonstrated the value of this method in differentiating between papilloedema and pseudopapilloedema Their findings

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have been confirmed by several investigators (Dollery 1965 Hayreh 1968 Oosterhuis & Boen Tan 1969, Heydenreich 1973 and others) Since David in 1963 described the various pathological angiographic findings in papilloedema these have been studied in order to make an accurate and early diagnosis of optic disc oedema

Bynke & Åberg (1970) investigated the deep disc fluorescence in papilloedema and pseudopapilloedema by means of blue filter ophthalmoscopy after intra venous injection of fluorescein In 4 of 16 cases of papilloedema the fluorescence was faint and of the same order as in pseudopapilloedema It was concluded that the method is not entirely reliable Dollery et al (1965) using fluorescence photography studied disc fluorescence by densitometry and found that 2 of 23 cases with papilloedema were within normal range

The purpose of this study was to test the reliability of fluorescence fundus angiography in order to 1) distinguish between pseudopapilloedema and oedema of the optic disc 2) diagnose early oedema of the disc and 3) investigate whether there exist any angiographic differences between various the causes of optic disc oedema

In this article papilloedema refers to disc oedema that is due to increased intracranial pressure

Material

The clinical material consists of 43 patients, 19 male and 24 female All patients except one were treated as in patients in various departments of the hospital

Table I

Patients with blurred optic disc divided into subgroups after a complete ophthalmological and neurological examination

	Total	♂	♀	Age mean	Range
Papilloedema	15	8	7	40	17–70
Optic neuritis	5	2	3	33	26–41
Disc associated with pseudo tumour cerebri (benign intra cranial hypertension)	2	0	2	29	25–33
Normal disc	7	2	5	36	16–61
Drusen of the disc	4	1	3	16	9–21
Ischaemic optic neuropathy	10	6	4	70	54–87

Fig 1

Incipient papilloedema Fluorescein angiogram (early arteriovenous phase) showing microaneurysms and numerous superficially dilated capillaries extending over the disc margin

chiefly the departments of ophthalmology neurology and neurosurgery The patients were referred to the ophthalmological department because of blurred optic disc margins After complete ophthalmological and neurological examinations including electro encephalography and X ray of the skull supplemented by cerebral angiography and pneumoencephalography in those cases suspected *of having intracranial disease the material is divided into the following sub* groups 1) Papilloedema 2) Optic neuritis 3) Disc associated with pseudotumour cerebri (benign intracranial hypertension) 4) Normal disc 5) Drusen of the disc and 6) Ischaemic optic neuropathy (Table I)

Methods

The fundus angiograms were performed with a Zeiss Fundus Camera. The film used was Kodak Plus X pan After injection of 5 ml sodium fluorescein solution (100 mg/ml) into an antecubital vein the angiograms were taken automatically every second during the transit of dye and then [illegible] 5 10 15 20 30 and sometimes 60 min after the injection The filter combination is important in order to obtain satisfactory angiograms We have found Zeiss interference filter KP 500 as excitation filter combined with Kodak Wratten No 15 as barrier filter useful in eliminating pseudofluorescence

Results

Oedema of the optic disc shows three characteristic signs irrespective the cause of oedema 1) Dilated capillaries 2) Microaneurysm formation 3) Leakage of dye producing late fluorescence of the disc and adjacent retina

The superficially dilated capillaries have a typical radial arrangement most pronounced in the superior and inferior temporal part of the peripapillary retina They nearly always extend over the disc margin (Fig 1) The capillaries are straight in moderate oedema in more advanced cases they become tortuous The degree of capillary changes is mostly correlated to the extent of oedema In addition in patients with a rapidly developing papilloedema the changes are more pronounced than in patients with slowly progressive oedema of the same prominence

Microaneurysms to a greater or lesser degree are always found in cases of optic disc oedema The microaneurysm formation is located at the whole disc area and also to the area of capillary dilatation (Fig 1)

The late fluorescence is an expression of abnormal capillary permeability In evaluating the degree of leakage it is absolutely necessary to have angio grams taken at least 10 min after injection In our experience most angiographic

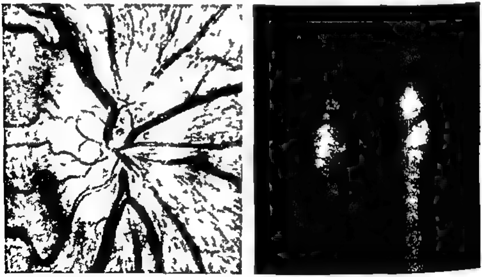

Fig 2 A and B

A Incipient papilloedema Fundus photograph

B Angiogram late phase (10 min) demonstrates pathological fluorescence in a circular pattern at disc margin

Fig 3 A and B

A Oedematous optic disc with 3 D prominence due to pseudotumour cerebri Angiogram (early arteriovenous phase) showing numerous dilated capillaries and microaneurysms B Angiograms late phase (10 min) showing faint late fluorescence which is almost entirely restricted to the oedematous disc area

data are obtained in the course of 15 min and for practical diagnostic procedures the final picture should be taken 15 min after injection of dye

The degree of late fluorescence of the disc and the leakage of fluorescein into the adjacent retina is usually considerable both in papilloedema and in optic neuritis

Six of our 15 cases of papilloedema were at the very early stage which made an ophthalmological differentiation from a normal disc highly uncertain In three of them there was no doubt about the pathologically late fluorescence In the other three cases the late fluorescence was very faint In these cases however the fluorescence had a special circular location along the disc margin making possible a clearly distinction between that and normal disc fluorescence (Fig 2 A and 2 B)

In our two cases of pseudotumour cerebri the late fluorescence was not marked and almost entirely restricted to the disc area (Fig 3 A and 3 B) This was in disproportion to the marked ophthalmoscopic and angiographic findings in these cases with a prominence of the disc of 3 D and marked capillary

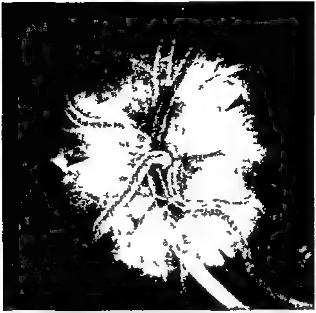

Fig 4

Drusen of the optic disc Angiogram late phase (10 min) showing fluorescence in circular structures near disc margin (arrows indicate drusen)

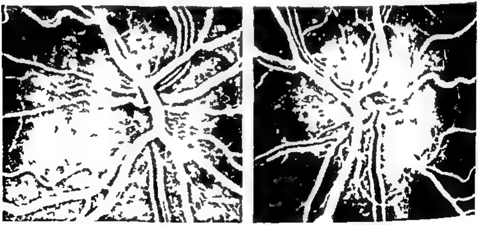

Fig 5 A and B

A Oedematous optic disc due to optic neuritis Angiogram (early arteriovenous phase) showing moderately dilated capillaries and no microaneurysms

B Oedematous optic disc of same magnitude as in Fig 5 A due to increased intracranial pressure In contrast to Fig 5 A the angiogram reveals numerous microaneurysms

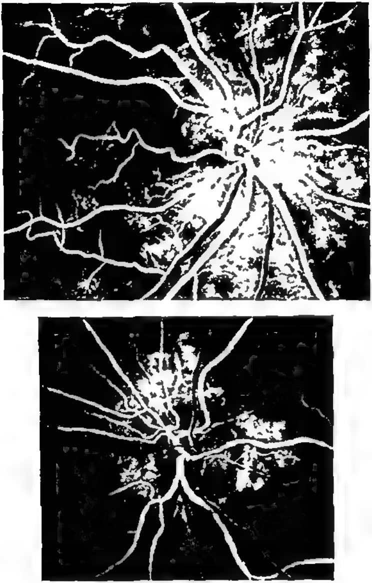

Fig [illegible] *1 and B*

A Ischaemic optic neuropathy (?2 year old woman) due to temporal arteritis Visual acuity [illegible] 60 with inferior nasal quadrant defect in visual field Angiogram (arteriovenous phase) showing filling defect of the optic disc and adjacent retina

[illegible] Ischaemic optic neuropathy (75 year old woman) of [illegible] days duration with no evidence of temproal arteritis Visual acuity was hand motion in temporal part of visual field Angiogram (arterial phase) showing almost no filling of the optic disc and chorioidea Note the arteriosclerotic vessels

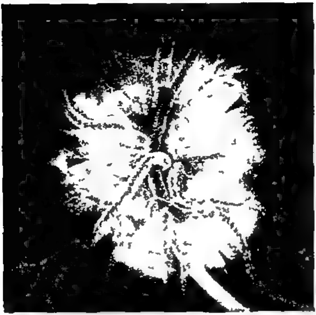

Fig 4

Drusen of the optic disc Angiogram late phase (10 min) showing fluorescence in circular structures near disc margin (arrows indicate drusen)

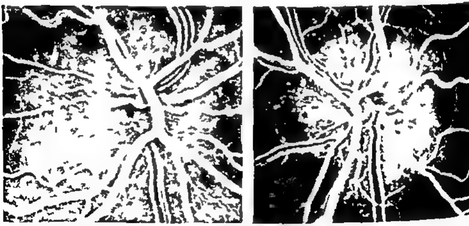

Fig 5 A and B

A Oedematous optic disc due to optic neuritis Angiogram (early arteriovenous phase) showing moderately dilated capillaries and no microaneurysms

B Oedematou optic disc of same magnitude as in Fig 5 A due to increased intracranial pressure In contrast to Fig 5 A the angiogram reveals numerous microaneurysms

we however compare the angiogram of optic neuritis (Fig 5 A) and papillodema (Fig 5 B) there are some minor differences With the same degree of prominence and compared in the same angiographic phase the capillary dilatation is about the same but the microaneurysms are more pronounced in papilloedema than in optic neuritis

Ischaemic optic neuropathy was diagnosed in 10 out of 43 patients The optic lesion was due to temporal arteritis in four patients and arteriosclerosis in six patients In all these cases we found filling defects of the optic disc and chorioidea The filling defects were either sectorial (Fig 6 A) or total (Fig B) Among our 10 patients five showed angiographic evidence of total defects three showed filling defects in either the nasal or temporal part of the optic disc and adjacent chorioidea while two showed quadrant defects During the 2–3 weeks after the vascular occlusion the ischaemic optic disc revealed evidence of reactive hyperaemia manifested as capillary dilatation micro aneurysms and leakage of dye (Fig)

Discussion

Fluorescence of the normal disc is seen to consist of at least two components We have sometimes observed fluorescence of the disc before the filling of the retinal arteries and simultaneously with the filling of the chorioidal vessels The disc fluorescence is greatly enhanced when the retinal capillaries are filling *Hayreh (1969) contributes the first component to fluorescence of the prelaminar* region the second to the fluorescence of the surface layer of the optic head

The fluorescein angiographic findings in optic disc oedema are characterized by capillary dilatation microaneurysms and leakage of dye We have found these changes to be most marked when associated with acute elevation of the intracranial pressure In slowly growing intracranial tumours and especially in benign intracranial hypertension (pseudotumour *cerebri*) there is *dispropor* tion between capillary changes and leakage of dye

The dilated superficial capillaries are radially arranged and cross the optic disc margin They are especially numerous along the temporal part of the disc They probably correspond to the radial peripapillary capillaries (Michaelson & Campbell 1940 Henkind 1967)

Some authors have claimed that it is not possible to detect early papilloedema using fluorescein fundus angiography This is not our experience The late fluorescence however can vary considerably Usually there is no doubt about the pathological late fluorescence which extends over the disc margin This was clearly demonstrated in 12 of 15 cases In three cases all with incipient

papilloedema the late fluorescence was very faint with no obvious leakage to the peripapillary retina These could erroneously have been classified as normal discs especially when either the quantitative method of Dollery et al (1965) or fluorescein ophthalmoscopy was used In these patients the late fluorescence occurred at the disc margin previously observed by Hayreh (1968) in very early papilloedema In addition when the disc capillaries were examined we found a pathologically increased capillary network This is often the first sign in very early papilloedema and is in agreement with Oosterhuis & Boen Tan (1969) Due to very rapid passage of dye the interpretation of very early papilloedema is dependent on fluorescein fundus photography and not fluorescein ophthalmoscopy Both the capillary changes and leakage of dye must be analysed in order to evaluate the angiograms correctly

Optic disc oedema associated with pseudotumour cerebri revealed a marked disproportion between the great capillary changes and minimal leakage of dye As we have only examined two patients however more experience will be necessary to decide whether this is a characteristic angiographic picture

This study shows minor differences between papilloedema and optic neuritis With same degree of prominence more pronounced microaneurysm formation is found in papilloedema The late fluorescence however is the same The fluorescein angiographic picture of papilloedema is different in rapid and slowly growing oedema and also in longstanding oedema Such factors will obscure the minor differences to such a degree that in a given patient it is impossible to differentiate disc oedema due to increased intracranial pressure from neuritis of the optic nerve

Ischaemic optic neuropathy is a clinical entity with characteristic findings (Hayreh 1975) In all our 10 patients we could find affection of the ciliary circulation producing filling defects of the optic disc and chorioidea either total or segmentally It is important to notice that the angiographic findings are dependent upon the time which has elapsed between the onset of the disease and the examination After 2–3 weeks we observed reactive hyperaemia of the optic disc with leakage *of dye in the same sector* as the filling defect This hyperaemia can be demonstrated up to 10 weeks after the beginning of the disease Ischaemic optic neuropathy can be clearly differentiated from other causes of optic disc oedema It is however important to notice that this characteristic angiographic picture is similar in appearance regardless of whether the ischaemic optic neuropathy is caused by temporal arteritis or by arteriosclerosis

Pseudopapilloedema sometimes leads to misinterpretation and an erroneous diagnosis of papilloedema Drusen of the disc congenital tortuosity of retinal vessels and a congenital excess of glial tissue can give rise to similar confusion

Drusen are characterized by 1) normal capillary network and passage of dye 2) gradually increasing fluorescence during the first minutes especially near disc margin Fluorescein fundus angiography is especially suitable in differentiating pseudopapilloedema from oedema of optic disc

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References

Bynke H G & Åberg L (1970) Differentiation of papilloedema from pseudopapilloedema by fluorescein ophthalmoscopy *Acta ophthal (Kbh) 48* 152–158

David N J et al (1963) *Fluorescence photography of retinal vessels and optic discs in papilledema Trans amer neurol Ass 88* 155–158

Dollery C T et al (1965) Studies by fluorescence photography of papilledema in malignant hypertension *J Neurol Neurosurg Psychiat 28* 241–246

Hayreh S S (1968) Pathogenesis of oedema of the optic disc *Docum ophthal 24* 289–411

Hayreh S S (1969) Blood supply of the optic nerve head and its role in optic atrophy glaucoma and oedema of the optic disc *Brit J Ophthal 53* 721–748

Hayreh S S (1975) *Anterior ischaemic optic neuropathy* Springer Verlag Berlin Heidelberg New York pp 145

Henkind P (1967) Radial peripapillary capillaries of the retina I Anatomy human and comparative *Brit J Ophthal 51* 115–123

Heydenreich A et al (1973) Differentialdiagnose von Papillenveranderungen mit Fluorescein *Klin Mbl Augenheilk 163* 131–139

Michaelson I C & Campbell A C P (1940) The anatomy of the finer retinal vessels and some observations on their significance in certain retinal diseases *Trans ophthal Soc U K 60* 71–112

Miller S J H et al (1965) Fluorescein fundus photography in the detection of early papilloedema and its differentiation from pseudopapilloedema *Lancet 2* 651–654

Novotny H R & Alvis D L (1961) Method of photographing fluorescence in circulating blood in the human retina *Circulation 24* 82–86

Novotny H R & Alvis D L (1960) A method of photographing fluorescence in circulating blood of the human eye *Amer J Ophthal 50* 176

Oosterhuis J A & Boen Tan T N (1969) Fluorescein angiography in papilloedema and pseudopapilloedema *Ophthalmologica 159* 96–110

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TRAUMATIC HYPHAEMA TREATED WITH THE ANTIFIBRINOLYTIC DRUG TRANEXAMIC ACID II

BY

THORKILD BRAMSEN

During the year 1976 (January 1st to December 31st) 75 patients consecutively admitted to the eye department of Århus Kommunehospital with traumatic hyphaema were treated with the antifibrinolytic drug tranexamic acid. No secondary haemorrhage occurred. The patients were not confined to bed. The eyes were not patched and the activities of the patients were not restricted.
In a previous series from 1975 where the patients were confined to bed but otherwise treated identically with tranexamic acid one out of 72 patients had a secondary haemorrhage. When the two materials are combined one out of 147 patients had a secondary haemorrhage corresponding to 0.68 %.

Key words: traumatic hyphaema – secondary haemorrhage – fibrinolysis – therapy – tranexamic acid

In a study of 72 patients with traumatic hyphaema treated with an antifibrinolytic drug (Bramsen 1976) an incidence of secondary haemorrhage of 1.4 % was found. This low incidence made it tempting to continue the investigations by treating patients with the antifibrinolytic drug but avoiding the bed rest. The bed rest is inconvenient for both the patients and the hospital staff and the demonstration of its insignificance would be a great practical step forward.

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It is conceivable that the fibrinolytic activity following trauma has no relation to body rest Assuming that the secondard haemorrhage is due to a fibrinolytic decomposition of a clot in a vessel before healing then provided that the fibrinolytic activity is effectively inhibited the incidence of secondary haemorrhage should be unchanged even when the patients are out of bed

Material

The material comprised 75 patients with traumatic hyphaema consecutively admitted to the Department of Ophthalmology during the period January 1st to December 31st 1976 Excluded from the material were those patients with only a haemorrhagic aqueous flare None of the patients were admitted with a secondary haemorrhage. The 75 patients comprised 63 males (average age 24 1 years range 1 to 70 years) and 12 females (average age 19.5 years range 2 to 69 years) The patients were admitted either from the casualty department or from a general practitioner A few were referred by ophthalmologists

The associated ocular lesions can be seen from Table I In this table the associated lesions from the group treated in 1975 is included for comparison

Table I
Lesions associated with traumatic hyphaema

	No of patients 1975 group	No of patients 1976 group
Subconjunctival haematoma	[illegible]	11
Corneal erosion	14	16
Pupillary changes	3?	36
Iridodialysis	2	3
Increased intraocular tension	3	4
Traumatic cataract	1	3
Retinal haemorrhage	[illegible]	[illegible]
Central retinal oedema	7	9
Choroidal rupture	1	3
No associated lesions	8	9
No of patients	72	5

Methods

Patients with hyphaema remained in hospital for five days. The only treatment was peroral tranexamic acid (Cyklokapron®). The dose was 25 mg/kg body weight three times daily for 6 days. Tranexamic acid was administered in tabletform. Mydriatics and topical steroids were not used. Acetazolamide was given if a rise in intraocular pressure (> 30 mmHg) developed. The patients were allowed to walk around in the department to read and to watch television. Eye patching was not used. Biomicroscopy, ophthalmoscopy, measurement of intraocular pressure and determination of visual acuity were performed on the 5th and 12th day. At the 12th day patients over 10 years of age were examined gonioscopically with special regard to the presence of synechias at the site of the primary clot.

In the investigation from 1975 the group was compared with a group of patients from the period 1965–68 in which the incidence of secondary haemorrhage was 6.7 %. A comparison between these two groups treated with and without tranexamic acid and the series from 1976 is shown in Table II.

Results

Among the patients admitted in 1976 no case of secondary haemorrhage occurred. In the investigation from 1975 the incidence of secondary haemorrhage was 1.4 %.

Follow up examination on the 12th day after the trauma showed visual acuities as shown in Table III. The results from 1975 can be seen in the same table. No cases of iritis or increased intraocular tension were found at this time.

Table II

Material	1976 group	1975 group	1965–68 group
No. of patients	75	72	155
Males	63	60	104
Females	12 (16.0 %)	12 (16.6 %)	31 ([illegible]9 %)
Average age males (years)	24.1	20.8	21.5
Average age females (years)	19.5	20.1	15.6
Average stay (days)	5.0	5.0	4.8

Table III
The visual acuity 12 days after the trauma in the two groups treated with tranexamic acid

1975 group		1976 group	
Visual acuity	No of patients	Visual acuity	No of patients
≥ 1.0	[illegible]	≥ 1.0	56
0.5–0.9	8	0.5–0.9	10
0.3–0.4	3	0.3–0.4	4
0.1–0.3	4	0.1–0.3	4
< 0.1	0	< 0.1	1

As mentioned patients over 10 years of age were examined with special regard to the presence of goniosynechias at the site of the primary clot. Synechias were found in 6 out of 62 patients. On the 12th day none of these patients had any symptoms from the synechias.

Discussion

In the material from 1975 the incidence of secondary haemorrhage was 1.4 %, the lowest reported so far. In this material from 1976, where all the patients were out of bed and the only treatment consisted of Cyklokapron®, there were no cases of secondary haemorrhages. In the series from 1975 the patient with the secondary haemorrhage was admitted to the hospital 36 h after the eye trauma. Tranexamic acid was administered for six days after the occurrence of the secondary haemorrhage. On the 12th day the visual acuity was 1.0 and the hyphaema had disappeared.

The two materials from 1975 and 1976 are comparable: the number of patients were almost equal (72 to 75). The distribution of age and sex and the severity of the traumas are also comparable as seen in Tables I and II. It may therefore be concluded that bed rest is of no importance when the fibrinolysis is inhibited. When the two materials are combined, a total of 147 patients were treated with tranexamic acid with only one case of secondary haemorrhage, corresponding to an incidence of 0.[illegible] %.

Crough & Frenkel (1976) made a double blind study of 59 patients with traumatic hyphaema. 32 patients were treated with the antifibrinolytic drug

aminocaproic acid and in this group there was one secondary haemorrhage (this patient suffered from sickle cell trait) 27 patients were given placebo and in this group there were 9 secondary haemorrhages so these authors also found a convincing effect of an antifibrinolytic treatment of traumatic hyphaema

Fritch (October 1976) reported a study of 50 patients with traumatic hyphaema He found a 6 % incidence of secondary haemorrhage when the patients were treated with bed rest elevation of the head and binocular patching for five days The authors claims that only a few series approach such a low incidence In our material where the patients were treated with Cyklokapron® there is a much lower incidence and in the period where all the patients were out of bed the incidence was 0 % The only recorded side effect of the treatment in our series was slightly increased peristaltic motion and this has not resulted in any discontinuation of treatment

An antifibrinolytic treatment of traumatic hyphaema seems at present to be the treatment of choice

From January 1st 1977 patients with traumatic hyphaema admitted to our department are being treated solely with tranexamic acid To determine whether there exists any difference between out patients and hospitalisized patients when both groups are treated with tranexamic acid we from January 1st 1977 will by lot treat half of the patients as out patients

References

Bramsen T (1976) Traumatic hyphaema treated with the antifibrinolytic drug tranexamic acid *Acta ophthal (Kbh) 54* 250–256

Crouch E R & Frenkel M (1976) Aminocaproic acid in the treatment of traumatic hyphaema *Amer J Ophthal 81* 355–360

Fritch C D (1976) Traumatic Hyphaema *Ann Ophthal 8* 1223–1225

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ON THE MOLECULAR COMPOSITION AND PHYSICO CHEMICAL PROPERTIES OF THE PSEUDO EXFOLIATION MATERIAL

BY

MARTIN DAVANGER

The protein tracer peroxidase has been found to be excluded from pseudo exfoliation (PE) material But after the treatment of the PE material with cetylpyridinium chloride peroxidase was found to penetrate into the material This observation seems to support the concept that the PE material is a gel of proteoglycans from which peroxidase is excluded by an excluded volume effect

Microperoxidase was found to penetrate into the superficial parts of the (untreated) PE material and to be regularly distributed according to two different patterns 1) along the PE fibrils and 2) along lines in the inter fibrillar matrix lines which can not be seen without the presence of micro peroxidase At both locations the microperoxidase reaction product was found at regular intervals with spacings of about 55 nm The interpretation is that both the fibrils and the interfibrillar matrix are composed of the same kind of long extended linear proteoglycan complexes but with a different arrangement and density

Key words pseudo exfoliation – mucopolysaccharide – proteoglycan – excluded volume effect – horse radish peroxidase – microperoxidase – lens

There is reason to believe that the pseudo exfoliation (PE) material on the anterior lens surface either consists of or contains mucoproteins or proteo glycosaminoglycans (acid mucopolysaccharides · proteoglycans) This concept

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is based upon histochemical investigations with light microscopy (Dvorak-Theobald 1954, Arnesen et al. 1963, Horven 1966, Bertelsen 1966) and on light and electron microscopy of specimens stained *en bloc* with Ruthenium Red and Alcian Blue (Davanger & Pedersen 1975).

One of the properties of proteoglycans is that in solution and in gel form they demonstrate the so-called „excluded volume effect". The basis of this effect is that each proteoglycan molecule occupies a relatively large space, a volume from which other macromolecules are excluded (Laurent 1972, 1968, 1963).

It has been shown that the protein tracer horse radish peroxidase does not penetrate into the PE material (Davanger & Pedersen 1975). The possibility that this phenomenon can be seen as an excluded volume effect of proteoglycans of the PE material is considered.

This explanation is relevant only if the proteoglycans are present in a gel form.

Proteoglycans in gel form are precipitated by polyvalent cations such as cetylpyridinium chloride (CPC) (Scott 1961, 1956, 1955, Hedbys 1961, Matukas et al. 1967). If the PE material either contains or consists of proteoglycans in gel form, it should be influenced by CPC, and the excluded volume effect might be eliminated by this treatment. To study whether this is the case, the penetration of peroxidase into the PE material after treatment of this material with CPC was examined.

As a further characterization of the physico-chemical properties of the PE material, it has been examined whether the tracer enzyme microperoxidase enters into the material. The molecular dimensions of this tracer are smaller than those of horse radish peroxidase: mol. weight 1900 vs. 40 000, molecular diameter about 2 nm vs. 4.5 nm (Vegge et al. 1971, Feder 1971).

Materials and Methods

The lenses used in this study were obtained by cataract cryo-extraction from eyes in which pseudo-exfoliation was found by clinical slit lamp examination prior to the operation. The lenses were processed immediately after the extraction. In all experiments the reactions have been followed through the dissecting microscope, and care has been taken to see that the anterior lens surface was facing upwards during the reactions and the fixation procedures.

Experiments with CPC. Four lenses were suspended for $^1/_2$–$1^1/_2$ h in a Krebs bicarbonate Ringer solution with glucose at 5 mg/ml (pH 7.4), containing 2 mM (0.717 mg/ml) CPC. Thereafter the lenses were rinsed in Ringer and placed in a 0.25 % solution of commercial horse radish peroxidase (Sigma type II) in Ringer for $^1/_2$–1 h. After

Fig 1

PE material treated first with CPC thereafter with peroxidase Peroxidase reaction product is seen as a cloudy electron dense material along the PE fibrils
x 107 000 bar = 100 nm

a further brief rinsing the lenses were incubated for 1/2–2 h in tris HCl buffered diaminobenzidine H_2O_2 solution pH 7.6 (Karnowsky 1967). All these reactions took place at room temperature. After rinsing in isotonic phosphate buffer pH 7.4 the lenses were fixed for 2 h at 4°C in 2.5 % glutaraldehyde in 0.1 M phosphate buffer pH 7.4 and after new rinsing in buffer for 2 h in 1 % OsO_4 in Millonig's phosphate buffer pH 7.4. After dehydration in graded ethanol solutions pieces of the lens capsule from the area of the peripheral band and the central disc were carefully dissected under a dissecting microscope while the lenses were submerged in 100 % ethanol. That part of the lens surface which had been frozen and deformed during the extraction was avoided. The specimens were embedded in Epon 812, sectioned and examined with light and electron microscopes as described earlier (Davanger & Pedersen 1975).

Two other lenses were treated as described above with the exception that the suspension in peroxidase was omitted. These lenses served as control of the effect of peroxidase.

Experiments with microperoxidase. Four lenses with PE were suspended immediately after the extraction in a 0.25 % solution of commercial microperoxidase (Sigma No M 6756) in Ringer's solution for 40 min to 3 h. The further processing was as described above.

Results

Experiments with CPC and peroxidase. No influence of CPC on the PE material could be observed by examination with the dissecting microscope before the incubation in the diaminobenzidine H_2O_2 solution. During the incubation the material obtained a more intense dark brown colour than was seen without the CPC treatment.

Light microscopy of sections confirmed that the PE material itself had obtained a brown colour and not only a dark coating as seen after the treatment with peroxidase without exposure to CPC (Davanger & Pedersen 1975).

Marked influence of CPC was also demonstrated by the electron microscopical examination (Fig. 1). Irregular clouds of electron dense substance were seen throughout the PE material. This concerns both the PE excrescences of the peripheral band and the material of the central disc. Because of the cloudy staining the PE fibrils could only with difficulty be identified; the cloudy material seemed to be most dense near the fibrils. Relative electron lucent areas with irregular forms were present.

The treatment with CPC and diaminobenzidine H_2O_2 only did not influence the light and electron microscopical picture of the PE material. The cloudy material described above was not present in the specimens in which suspension in the peroxidase solution was omitted.

Experiments with microperoxidase without CPC. A dense material, obviously a microperoxidase reaction product, was by electron microscopy found in the

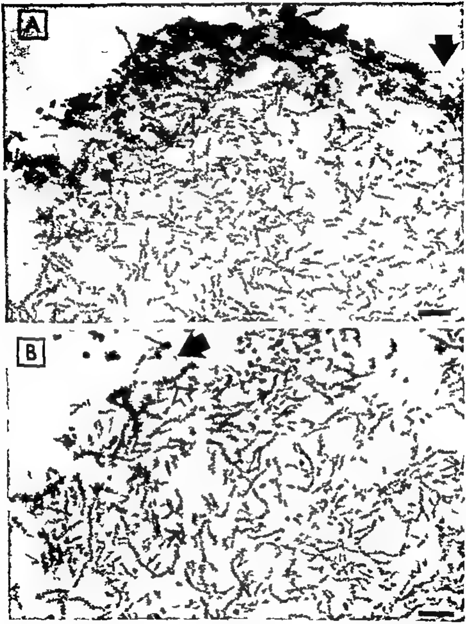


Fig 9

PE material with microperoxidase reaction product in its superficial parts Granules forming dotted lines (black arrows) and exaggeration of the cross bands of the fibrils (white arrow) A ×16 500 bar = 0.5 μm B ×18 000 bar = 0.5 μm


A
B

superficial parts of the PE material as well as on its surface (Fig 2) This concerns both the peripheral band and the central disc The quantity of the reaction product decreased gradually and rapidly from the surface inwards and in most of the material no sign of the tracer was found

A striking and remarkable finding was that most of the microperoxidase reaction product was regularly and not randomly distributed and according to two different patterns 1) along the PE fibrils and 2) along straight or slightly bent lines in the interfibrillar matrix lines which were not seen without the presence of the microperoxidase reaction product (Figs 2 3 and 4)

The reaction product both along the fibrils and in the matrix was found at intervals with regular spacings The period was about *53* nm which is the same as the distance between the well known cross bands of the PE fibrils (Bertelsen et al 1961 Ringvold 1969)

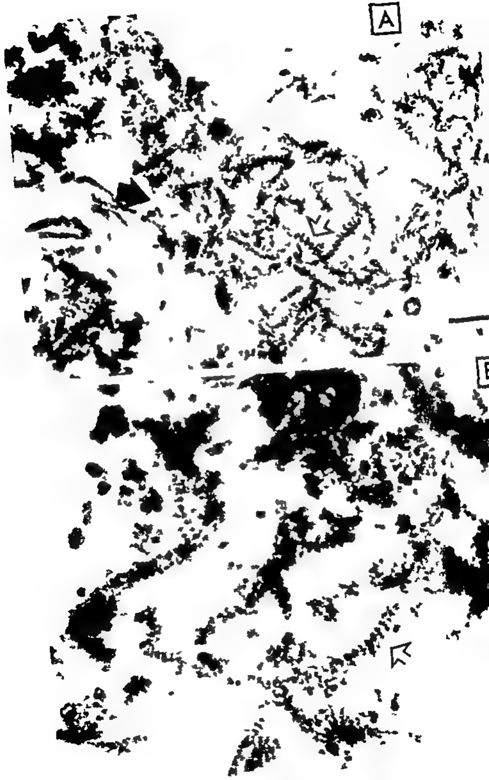
The reaction product along the PE fibrils could be so abundant and so regularly distributed that the fibrils could give the impression of being con structed by electron opaque discs up to 130 nm in diameter piled to a cylinder and separated by electron lucent interspaces (Fig 3 B) At other locations there was less reaction product and its presence was disclosed by exaggeration of the cross bands of the PE fibrils (Fig 3 A)

In the interfibrillar matrix the reaction product formed spherical granules with a rather uniform size and diameter of about 30 nm These granules were arranged like beads on a string and they formed dotted lines up to one μm long The lines were straight or slightly bent and they did not branch The center to center distance between the granules was rather constant about 53 nm No obvious pattern could be seen in the arrangement of the dotted lines relative to each other or to the PE fibrils

In general it was not difficult to distinguish between the two patterns of distribution of the microperoxidase reaction product in spite of the similar *periodicity of the spacings along the PE fibrils and in the interfibrillar matrix*

Fig 3

PE material with microperoxidase reaction product A Granules forming dotted lines in the interfibrillar matrix (black arrow) and exaggeration of the cross bands of the fibrils (white arrow) B *PE fibrils with coating of microperoxidase reaction product* forming marked cross bands (white arrow) A ×25 000 bar = 0.5 μm B ×35 000 bar = 0.5 μm


A

Discussion

In the experiments described in this study CPC influences the PE material to make it penetrable for the tracer molecule horse radish peroxidase This effect is consistent with the concept that proteoglycans is a major part of the PE material It further indicates that the proteoglycans are in a gel state and it supports the hypothesis that the exclusion of peroxidase from untreated PE material may be described as an excluded volume effect

From the results of the experiments with microperoxidase without CPC it may be concluded that this small tracer molecule is not totally excluded from the PE material Space is available at regular intervals of about 53 nm along the PE fibrils at their cross bands and also with intervals of the same size along lines in the interfibrillar matrix

This seems to mean that linear molecules or molecular aggregates are present in the interfibrillar matrix aggregates which are not seen by routine electron microscopy Further it seems to indicate that the PE fibrils are composed of molecular chains which are similar to or identical with those present in the matrix

The reaction product of microperoxidase is formed before the fixation of the specimen It is difficult to imagine how the regular distribution of the microperoxidase reaction product along the PE fibrils could be arranged if these fibrils were not present as such in the natural state of the material There fore the possibility that the fibrils are formed during the fixation procedure seems to be ruled out

The observations described have been interpreted to reflect properties of the proteoglycans of the PE material Therefore some relevant characteristics of these substances will be described

The proteoglycan molecules are considered to be long linear chain and extended macromolecules constructed by a protein core or backbone to which are attached a number of glycosaminoglycan (polysaccharide) side chains in a comblike structure (Scott 1975 Winterburn 1974 Laurent 1972 Cessi & Bernardi 1965 Mathews 1965) A proteoglycan whose molecular configuration was studied electron microscopically by Rosenberg et al (1970) was found to have a linear non branching protein core to which were attached approximately 30 evenly distributed polysaccharide side chains The overall dimension of this molecule was approximately 100 × 300 nm

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Fig 4

PE material with microperoxidase reaction product located at the cross bands of the PE fibrils (white arrows) and forming dotted lines in the interfibrillar matrix (black arrow) A × 37 000 bar = 0.5 μm B × 35 000 bar = 0 5 μm

When they are in solution such basic units may entangle with other identical units to form macromolecular structures of higher complexity A molecule may intertwine for a part of its length with other molecules to form double or multi helices Each molecule may be involved in more than one helix This may result in the formation of a continuous three dimensional network the effect of which is a partial immobilization of the bulk fluid which is the main characteristic of a gel (Roughley 1975 Winterburn 1974 Rees 1972 Ogston 1970 Comper & Preston 1974)

The proteoglycans are expanded molecules which occupy relatively large domains volumes from which other large molecules are excluded depending on their size While large molecules may be totally excluded smaller molecules may swim through the domains more or less freely (Laurent 1972 1968 1963 Schubert 1965 Gerber & Schubert 1964 Scott 1975)

For sterical geometrical reasons the excluded volume phenomenon is relatively more pronounced for extended linear chain molecules than for molecules of similar molecular weight with a more spherical configuration (Laurent 1972 1968) The volume from which a proteoglycan molecule excludes other macromolecules may be a thousand times greater than the sum of its atomic volumes (Schubert 1965)

These general properties of proteoglycans may elucidate the observations described in this work The PE material is considered to be a gel formed by the entanglement of proteoglycan molecules into a continuous three dimensional cross linked network as in proteoglycan gels in general

It is proposed that the PE fibrils constitute the cross links in this network. The fibrils are thought to consist of dense aggregates of linear chain molecules They may represent the crystallites of the gel visible by the electron microscope as described by Finean (1967)

In the interfibrillar matrix the same chain molecules are thought to be present but here arranged at random and with low density because of a mutual excluded volume effect between the single molecular units The continuity of the network considered to be the basis of the gel state is created by some of the linear units taking part in the formation of more than one fibril

A schematic and simplified illustration of this hypothetic model of the composition of the PE material is seen in Fig 5

This model is consistent with the observation of Ringvold & Husby (1973) They found by electron microscopy at high magnification that the PE fibrils are composed of thin linear subunits lying side by side and loosely twisted together

The concept described of the ultrastructure of the PE material is best understood on the assumption that the material is formed by a gradual condensation

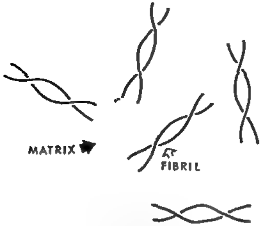

Fig 3

Hypothetical model of the molecular composition of the PE material schematic and simplified The PE material is considered to be a gel constructed by the entanglement of long linear proteoglycan complexes into a three dimensional network in which the PE fibrils are the cross links

to a gel state of molecules which have been dissolved in the aqueous The PE excrescenses on the lens and on several surfaces facing the posterior chamber have a typical architecture a bush shaped form and a feathery internal structure as seen by light microscopy They do not give the impression of being a randomly arranged collection of material This leads to the assumption that they are formed by condensation on the spot

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References

Arnesen K Sunde O A & Schultz Haudt S D (1963) Histochemical studies of the deposits of Busacca in eyes with glaucoma simplex and so called senile exfoliation of the anterior lens capsule *Acta ophthal (Kbh) 41* 80–84

Bertelsen T I (1966) Fibrillopathia epithelio capsularis The so called senile exfoliation or pseudo exfoliation on the anterior lens capsule *Acta ophthal (Kbh) 44* 73 –130

Bertelsen T I Drablos P A & Flood P R (1964) The so called senile exfoliation (pseudoexfoliation) of the anterior lens capsule a product of the lens epithelium. Fibrillopathia epitheliocapsularis *Acta ophthal (Kbh) 42* 1096–1113

Cessi C & Bernardi G (1965) The kinetics of enzymatic degradation and the structure of proteinpolysaccharide complexes of cartilage In *Structure and function of connective and skeletal tissue* Eds Fitton Jackson S Harkness R D Patridge S M & Tristam G R pp 152–156 Butterworths

Comper W D & Preston B N (1974) Model connective tissue systems A study of polyion mobile ion and of excluded volume interactions of proteoglycans *Biochem J 143* 1–9

Davanger M (1975) The pseudo exfoliation syndrome A scanning electron microscopical study I The anterior lens surface II The posterior chamber region *Acta ophthal (Kbh) 53* 809–833

Davanger M & Pedersen O O (1975) Pseudo exfoliation material on the anterior lens surface Demonstration and examination of an interfibrillar ground substance *Acta ophthal (Kbh) 53* 3–18

Dvorak Theobald G (1954) Pseudo exfoliation of the lens capsule Relation to true exfoliation of the lens capsule as reported in the literature and role in the production of glaucoma capsulo cuticulare *Amer J Ophthal 37* 1–12

Feder N (1971) Microperoxidase An ultrastructural tracer of low molecular weight *J Cell Biol 51* 339–343

Finean J B (1967) *Engstrom Finean Biological Ultrastructure* pp 96–101, 2nd ed. Academic Press New York and London

Gerber B R & Schubert M (1964) The exclusion of large solutes by cartilage protein polysaccharide *Biopolymers 2* 259–273

Hedbys B O (1961) The role of polysaccharides in corneal swelling *Exp Eye Res 1* 81–91

Hørven I (1966) Exfoliation syndrome A histological and histochemical study *Acta ophthal (Kbh) 44* 790–800

Karnovsky M J (1967) The ultrastructural basis of capillary permeability studied with peroxidase as tracer *J Cell Biol 39* 213–236

Laurent T C (1972) The ultrastructure and physical chemical properties of interstitial connective tissue *Pflugers Arch ges Physiol 336 (Suppl)* S21–S42

Laurent T C (1968) The exclusion of macromolecules from polysaccharide media In *The chemical physiology of mucopolysaccharides* Ed Quintarelli C pp 153–170 Little Brown & Co Boston

Laurent T C (1963) The interaction between polysaccharides and other macromolecules 5 The solubility of proteins in the presence of dextran *Biochem J 89* 253–257

Mathews M B (1965) A comparative study of acid mucopolysaccharide protein complexes In *Structure and function of connective and skeletal tissue* Eds Fitton Jackson S Harkness R D Patridge S M and Tristam G R pp 181–191 Butterworths

Matukas V J Panner B J & Orbison J L (1967) Studies on ultrastructural identification and distribution of protein polysaccharide in cartilage matrix *J Cell Biol 32* 365–377

Ogston A G (1970) The biological functions of the glycosaminoglycans In *Chemistry and molecular biology of the intercellular matrix* Ed Balazs E A pp 1231–1240 Academic Press London

Rees D A (1972) Shapely polysaccharides *Biochem J 126* 257–273

Ringvold A (1969) Electron microscopy of the wall of iris vessels in eyes with and without exfoliation syndrome (pseudoexfoliation of the lens capsule) *Virchows Arch Abt A Path Anat 348* 328–341

Ringvold A & Husby G (1973) Pseudo exfoliation material – an amyloid like substance *Exp Eye Res 17* 289–299

Rosenberg L Hellmann W & Kleinschmidt A (1970) Macromolecular models of protein polysaccharides from bovine nasal cartilage based on electron microscopic studies *J Biol Chem 245* 4123–4130

Roughley P J (1975) Helix formation Its involvement in the formation of gel structures *Trans ophthal Soc U K 95* 369–371

Schubert M (1965) Proteinpolysaccharides entanglement and excluded volume In *Structure and function of connective and skeletal tissue* Eds Fitton Jackson S Harkness R D Patridge S M and Tristam G R pp 124–131 Butterworths

Scott J E (1975) Composition and structure of the pericellular environment *Phil Trans R Soc Lond B 271* 235–242

Scott J E (1961) The precipitation of polyanions by long chain aliphatic ammonium salts *Biochem J 81* 418–424

Scott J E (1956) The preparation and fractionation of acidic polysaccharides using long chain quaternary ammonium compounds *Biochem J 62* 31P

Scott J E (1955) The solubility of cetylpyridinium complexes of biological polyanions in solution of salts *Biochim biophys Acta 18* 428–4 9

Vegge T Winther F O & Olsen B R (1971) Horseradish peroxidase in plasma studied by gel filtration *Histochemie 28* 16–22

Winterburn P J (19 4) Polysaccharide structure and function In *Companion to Biochemistry* Eds Bull A T L gnado J R Thomas J O and Tipton K F pp 307–341 Longman London

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A METHOD OF ISOLATING AND COLLECTING PSEUDO EXFOLIATION MATERIAL FROM EXTRACTED CATARACTOUS LENSES

BY

MARTIN DAVANGER

It has been observed that the pseudo exfoliation (PE) material on the surface of extracted lenses was not dissolved by a papain solution while the underlying lens capsule was digested This forms the basis of a method for isolating and collecting PE material The anterior lens surface was swept with a cilium after the lens had been suspended in a 5 % papain solution for 1/2–1 hour The PE material was loosened in flakes which adhered to the tip of the cilium and could be collected as a lump By light and scanning and transmission electron microscopy no contaminants could be seen and no damage to the PE material was disclosed

Key words pseudo exfoliation – lens – papain

One of the problems in the study of the pseudo exfoliation (PE) syndrome is that the PE material is found only in minute quantities Therefore the properties of the material have been studied almost exclusively with methods involving light and electron microscopy of eye tissue of which the PE material comprises only a very small part To the author s knowledge there are only two exceptions Ringvold (1970) collected PE material from the peripheral band on the anterior lens surface by rubbing it away from the moist lens with a pin before the lens capsule dried The material was examined with the electron microscope after negative staining Later the same author examined the amino

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acid composition of the PE material collected by the same method (Ringvold 1973)

One can imagine that the method is technically difficult that only a part of the material is collected and that there is a risk that the material collected may contain contaminants which was also shown to be the case (Ringvold 1973)

Obviously it would be of value that the PE material could be isolated and collected for further studies The most practical source seems to be lenses with PE extracted because of cataract

During experiments whose purpose was to study whether the PE material on whole fresh lenses could be dissolved by enzymatic digestion it was observed by using a dissecting microscope that the lens capsule was digested by papain which did not seem to affect the PE material If the lens was left undisturbed in a solution of papain for some hours at room temperature a more or less continuous membrane of PE material loosened itself from the anterior lens surface and floated in the solution

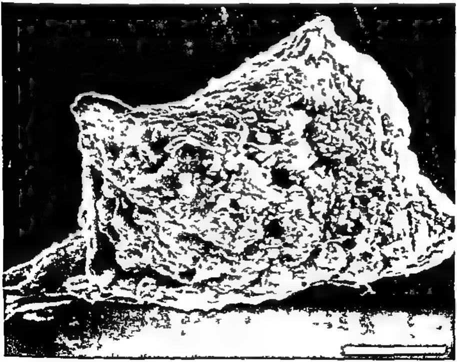


Fig 1
A lump of PE material sticking to the tip of a cilium collected after papain treatment of an extracted lens Scanning electron microscopy x 950 bar = 0 1 mm

Obviously this phenomenon may be used to isolate and collect PE material In the following account a simple procedure will be described together with the results of microscopical examination of the material collected

Material Methods and Results

Immediately after cataract cryo extraction lenses with PE were suspended in a 5 % solution of papain (Serva pract) in Ringer s solution at room temperature With a dissecting microscope it was controlled that the anterior lens surface was facing upwards The lenses were left undisturbed for ½–1 hour The PE material could then be loosened from the lens by carefully sweeping the lens surface with a cilium attached to a Pasteur pipette (as used in the handling of ultrathin sections for electron microscopy) The procedure was controlled with the help of a dissecting microscope at 10–16 times magnification

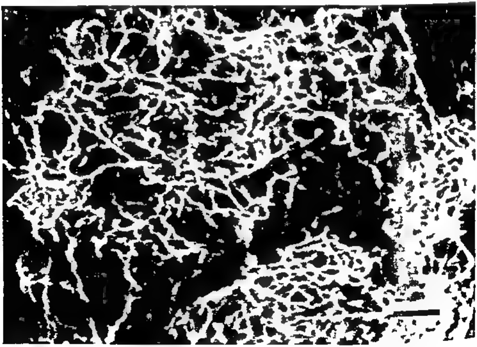


Fig 2

The surface of a lump of PE material collected after papain treatment of an extracted lens No influence of this treatment on the material can be seen Scanning electron microscopy x 12 000 bar = 1 μ

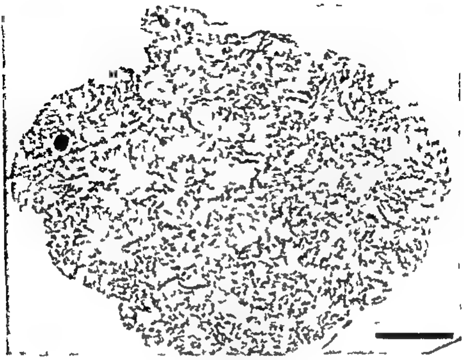


Fig 3

A section through PE material collected after papain treatment of an extracted lens A section of the cilium used is seen in the left part Light microscopy × 390 bar = 50 μ

and a focused beam of light directed obliquely along the lens surface The lenses were completely submerged in the solution and the material was not allowed to dry

The PE material was loosened in flakes of different sizes They were sticky and adhered to each other Thereby a small lump of PE material could be collected adhering to the tip of the cilium

The tendency to loosen in large flakes differed from one lens to another as did the quantity of the material obtained Typically an approximately spherical lump with a diameter of about 0 6 mm could be obtained from one lens This is about 0 1 mm^3 wet material The dry weight has not been determined

The PE material which adhered to the cilium seemed to be mucinous and half transparent and occasionally slightly brown in colour probably because of an admixture of pigment granules

To examine whether the lump really consisted of PE material whether

the material was altered by the treatment with papain and whether visible contaminants were present the material collected from two lenses were examined with the scanning electron microscope and from a further two lenses with the light and transmission electron microscope The methods of processing were the same as described earlier (Davanger & Pedersen 1975 Davanger 1975) It was found to be convenient to let the material adhere to the cilium during the processing the cilium could be used as a handle" and a marker

An overall view of a lump of PE material sticking to a cilium as seen by low magnification scanning electron microscopy is demonstrated in Fig 1 The surface of the material is seen under higher magnification in Fig 2 The surface is made up of fibrils similar to those seen by scanning electron microscopy on PE excrescences on surfaces facing the aqueous humour (Davanger 1975)

Light microscopy of a section through a lump of PE material collected as described above is seen in Fig 3 Most of the material was found to be amor

Fig 4
PE material after papain treatment No influence on the morphology of the PE material Electron microscopy × 43 000 bar = 0 5 μ

phous and without any specific characteristics but some typical bush like PE excrescenses could be seen

Transmission electron microscopy of the specimens showed the typical picture of PE material and no influence of the treatment with papain could be seen on the internal structure of the material (Fig 4)

Discussion

The basis of the method described is the observation that the lens capsule is dissolved by the treatment with papain while the PE material is not This has also been recorded by Bertelsen & Ehlers (1969) after their studies of enzymatic digestion of sections of lenses with PE

A relationship or similarity between PE and amyloidosis has been pointed out (Ringvold & Husby 1973 Meretoja & Tarkkanen 1975 Davanger & Pedersen 1975) On that background it is interesting to note that the standard procedure for obtaining amyloid material from amyloid laden organs is to digest the tissue with proteolytic enzymes which will dissolve most of the substances and damage the continuity of the tissue but will not dissolve the amyloid material (Sorensen & Binnington 1964)

A contamination of the PE material obtained as described with papain or with products of the enzymatic digestion of the lens capsule cannot be excluded nor can a certain enzymatic influence on the material be excluded However the material seems to be uninfluenced by the treatment as seen by light scanning and transmission electron microscopy Further it has been shown that large molecules are not admitted into the material (Davanger & Pedersen 1975 Davanger 1977) This may also be the case for papain molecules and may be the reason why the PE material is not digested

Isolation and collection of PE material as described may be a valuable step in the examination and characterization of the material and thereby in the understanding of the nature of the PE syndrome

References

Bertelsen T I & Ehlers N (1969) Morphological and histochemical studies on fibrillopathia epitheliocapsularis *Acta ophthal (Kbh)* 47 476–488

Davanger M & Pedersen O O (1975) Pseudo exfoliation material on the anterior lens surface Demonstration and examination of an interfibrillar ground substance *Acta ophthal (Kbh)* 53 3–18

Nosema Scandinavian authors have however tended to stick to the name *Nosema* even after 1971 In this paper we shall call the parasite *Encephalitozoon cuniculi* to be in conformity with international nomenclature

Systemic encephalitozoonosis (nosematosis) in the blue fox (*Alopex lagopus*) has been described from Finland (Kangas 1971) Sweden (Kull 1971) and Norway (Nordstoga 1972) The disease occurs within certain litters and frequently attacks all or the majority of the pups whereas their mothers remain in good health The animals show reduced appetite retarded growth thirst ataxia paresis of the hind limbs and convulsions Nordstoga & Westbye (1976) described polyarteritis nodosa like changes in the arteries of all organs studied At Gram staining the infecting organism could easily be demonstrated in the wall of the affected arteries

Some of the diseased fox pups from Norwegian farms appeared to be blind and a number of eyes were provided for histopathological study

Material and Methods

Seventeen eyes from 10 puppies approximately 3 months old were studied after fixation in 4 per cent aqueous formaldehyde solution for varying lengths of time The eyes were processed according to the standard technique adopted from the Armed Forces Institute of Pathology Washington, D C The globes measured about 15 x 13 mm

Paraffin embedded sections were stained with hematoxylin erythrosin saffran (HES) elastin van Gieson Martius Scarlet Blue (Lendrum Fraser Slidders & Henderson 1962) and a modified Gram method (Petri 1969) Characteristic lesions were photographed from different eyes

All animals whose eyes were studied revealed extra ocular lesions of encephalitozoonosis

Findings

Lesions were found in the short and long posterior ciliary arteries as well as in their uveal branches including those of the iris There were no convincing changes in the central artery of the retina There were however anastomoses between the juxta papillary choroidal branches of the short posterior ciliary arteries and the retinal vessels (Fig 1) Characteristic lesions were found in a few of the intraretinal vessels derived from the posterior ciliary arteries (Fig 2)

The retina was folded thickened oedematous and partly necrotic the degree of necrosis varying markedly between the eyes examined (Fig 1)

In 10 eyes the lens was lost during the tissue processing In six of the remaining seven eyes cataractous changes of varying degree were noted The

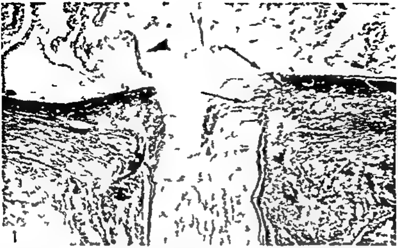


Fig 1

Posterior part of eye with optic nerve papilla and partly necrotic retina White arrows branch of posterior ciliary artery with lesions of the polyarteritis nodosa type Black arrows anastomoses between posterior ciliary and retinal vessels Large spear head artery in retina derived from posterior ciliary artery branch Small spear head central artery of optic nerve HES stain 23.5 ×

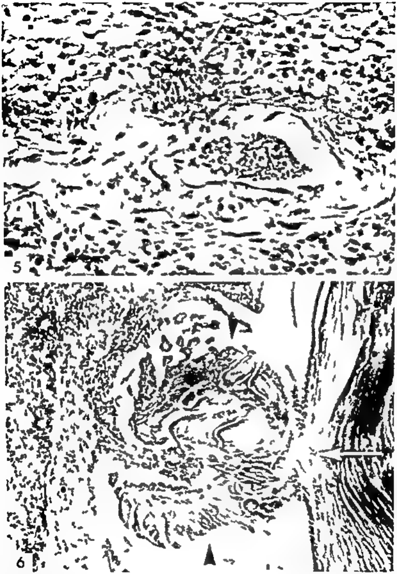
Fig 2

Retina close to papilla showing artery with characteristic lesions (black arrows) White arrow choroid at edge of papilla HES stain 235 x

Figs 3 and 4

3 Posterior ciliary artery penetrating into sclera Between spear heads destruction of arterial wall with fibrin like material and beginning aneurysm formation HES stain 115 ×

4 Artery of ciliary body Arrows fibrin like material in the wall HES stain 285 ×



Figs 5 and 6

5 Small artery of iris Arrow localized destruction of the wall gap filled with leuco cytes HES stain 285 x

6 Destruction of lens capsule (arrow) with extrusion of degenerated lens material (between spear heads) towards ciliary body with heavy inflammatory reaction in left part of picture HES stain 115 x

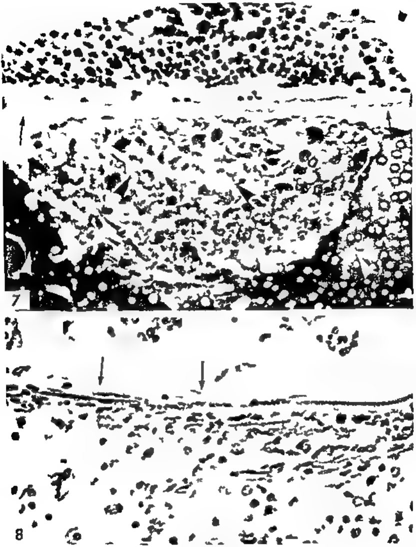
apparent absence of cataract in one eye is probably due to an insufficient number of sections

The arterial lesions were most clearly demonstrated in the vessels of the optic nerve sheath (Fig 1) and the posterior episclera and sclera (Fig 3) The lesions were segmental and nodular very closely copying the picture of polyarteritis (periarteritis) nodosa and affected all layers of the arterial wall in the advanced stages The internal elastic membrane was disrupted and there were localized accumulations of a material staining as fibrin in the intima and media (Figs 3 and 4) Swelling and proliferation of the endothelial cells were often noted as well as small superimposed thrombi The muscle layer underwent segmental destruction leading to aneurysm formation (Fig 3) There were localized and nodular infiltrates of lymphocytes plasma cells and histiocytes in the outer layers of the arterial wall including the adventitia Polymorphonuclear leucocytes occurred in relation to necrotic areas A few giant cells were seen but there were no eosinophils

Changes of the type described were found in the small arteries of the choroid, ciliary body (Fig 4) and iris (Fig 5) as well as in the retinal vessels which were obviously derived from the juxta papillary branches of the posterior ciliary arteries (Fig 2)

The modified Gram staining revealed the presence of slightly elongated Gram positive organisms with diameters between 1 and 3 μm occurring singularly or in clusters often located intracellularly in phagocytic cells (Figs 9 and 10) The parasites could be found in any layer of the arterial wall They were easily identified because of the polar vacuoles and correspond to organisms described by Nordstoga & Westbye (1976) in other fox organs whose identity was definitely established by means of electron microscopy

The lens changes are depicted in Figs 6–8 There was a thinning and breakage of the capsule of the anterior surface or of the equatorial region of the lens Correspondingly the lens fibers were liquefied or transformed into globular bodies which were often extruded into the posterior or anterior chamber with a surrounding tightly packed collection of leucocytes There was also an invasion of leucocytes into the damaged areas of the lens The adjacent ciliary body was oedematous disorganized and heavily infiltrated with leucocytes as can be seen in the left part of Fig 6 Huge numbers of the *Encephalitozoon* were present within the superficial areas of the cataractous lenses (Fig 11)



Figs 7 and 8

7 Anterior surface of lens with lens capsule (arrows) Subcapsular destruction of lens fibers with collection of macrophages and clusters of spores (black spear heads) which are not readily recognized with this staining White spear heads damaged lens material with vacuoles and globules HES stain 285 x

8 Detail of lens capsule of anterior surface Arrows indicate damaged and partly ruptured capsule HES stain 460 x

Figs 9 10 and 11

9 *Encephalitozoon* spores between spear heads in wall of posterior ciliary artery Arrows internal elastic membrane Modified Gram stain 1800 ×

10 Encapsulated spores (arrows) in wall of small artery of iris Modified Gram stain 1800 ×

11 Collection of spores in cataractous lens Modified Gram stain 3000 ×

Discussion

This report deals with two types of lesions in the eyes of blue foxes infected with *Encephalitozoon cuniculi* widespread vascular lesions of the polyarteritis nodosa type and cataract

In addition to the paper published by Ashton Cook & Clegg (1976) there are only few reports of eye lesions caused by the *Encephalito oon cuniculi* Ashton & Wirasinha (1973) described a case of keratitis in an 11 year old boy from Ceylon and a case of congenital and fatal encephalomyelitis and chorio retinitis in a 4 week old child with encephalitozoonosis was reported by Wolf & Cowen (1937) In a spontaneously infected mouse Perrin (1943) found peri vascular foci of lymphocytes as well as parasites in the retina

The cataract of the blue foxes with the generalized arterial disease described in the present paper is similar to the bilateral cataract in a rabbit which was reported by Ashton Cook & Clegg (1976) who did not find vascular lesions in these eyes They suggested that the parasites invade the lens epithelium in the equatorial region and that they are dependent upon the metabolism of the epithelial cells In our material the majority of the eyes with arterial lesions whose lens was not lost during the preparation were also cataractous but we do not know whether there is any link between the two manifestations of the infection in the eye

Nordstoga & Westbye (1976) in their study of blue foxes with encephalito zoonosis found polyarteritis nodosa like lesions in all organs examined not including the eyes The present report shows that the eyes were affected in the same way

Polyarteritis nodosa is a disease with wide spread manifestations attacking middle sized and smaller arteries of skeletal muscles and internal organs including the eye (Rahi & Garner 1976) The characteristic changes resemble those of the vasculitis associated with rheumatoid arthritis and systemic lupus erythematosus Immunocytochemical studies have revealed the presence of gamma globulin fibrinogen and complement in the walls of vessels with poly arteritis nodosa (Paronetto & Strauss 1962 Paronetto 1969) Gocke Hsu Mor gan Bombardieri Lockshin & Christian (1971) have found circulating complexes of Australia antigen and immunoglobulin in patients with polyarteritis nodosa proved by biopsy and in two of the patients in their series complexes of Australia antigen IgM and complement were demonstrated in the arterial wall There is thus indication that the immunological reaction which may be associated with polyarteritis nodosa is of the type III hypersensitivity nature

In this connection it is interesting that foxes with encephalitozoonosis have a marked hypergammaglobulinemia (Mohn & Nordstoga 1975) indicating a possible immunological pathogenesis of the arterial lesions

The aetiology of polyarteritis nodosa is not known The disease has been associated with bacterial particularly streptococcal infections (Rose 1957) and certain viral infections (Henson & Crawford 1974)

The finding of spores of *Encephalito oon* (*Nosema*) *cuniculi* in the arterial

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PERMEABILITY PROPERTIES OF THE TISSUES IN THE OPTIC NERVE HEAD REGION IN THE RABBIT AND THE MONKEY

An Ultrastructural Study

BY

TOR FLAGE

The distribution of the protein tracer horseradish peroxidase has been studied in the optic nerve head region in rabbits and monkeys by light and electron microscopy Following intravenous injection of the tracer the eyes were enucleated after varying time intervals Leaking out of the choroidal capillaries in the peripapillary choroid peroxidase rapidly spread to the adjacent sclera and to the intraneural connective tissue that is lamina cribrosa and the connective tissue surrounding the intraneural vessels The tracer then diffused from both the perineural and intra neural connective tissue into the adjacent optic nerve tissue This dif fusion could take place because the intercellular spaces in the astrocytic cell layer interposed between the connective and neural tissues were freely permeable to the tracer The present investigation confirms the presence of a defect in the blood optic nerve barrier in the optic nerve head The clinical importance of this defect in the permeability barrier is not known It may represent a predilection point for pathological events e g in retrobulbar neuritis

Key words blood optic nerve barrier – optic nerve head – permeability – peroxidase – monkey – rabbit – ultrastructure

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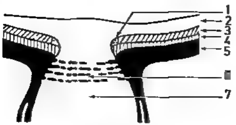

Fig 1
Optic nerve head region Intermediary tissue of Kuhnt (1) Retinal nerve fibre layer (2) Sensory retina (3) Choroid (4) Sclera (5) Lamina cribrosa (6) Optic nerve (7)

The central nervous system has tissue barriers that limit the diffusion of large molecular substances e g proteins from the blood and surrounding connective tissue into the neural tissue This is the blood brain barrier The same barriers are present in the optic nerve known as the blood optic nerve barrier and in the retina In certain areas of the brain the permeability barrier is incomplete Such areas are the choroid plexus the median eminence and area postrema In these locations large molecular substances in the blood may enter the neural tissue (Brightman et al 1970) The optic nerve head may represent an analogous area Previous investigations have shown that various tracers enter the optic nerve tissue in this location following intravenous administration (Rodriguez Peralta 1966 Grayson & Laties 1971 Tso et al 1975 Flage 1975) The aim of the present study is to characterize this defect in the blood optic nerve barrier in greater detail

Material and Methods

Part of the material and the procedure have been described before (Flage 1975) Horseradish peroxidase (Sigma type II) was used as an indicator of permeability properties of the tissues in the optic nerve head region This plant protein with a molecular weight of approximately 40 000 daltons and a diameter of about 4 5 nm has been widely used as an enzymatic histochemical tracer in light and electron microscopy (Graham & Karnovsky 1966 Karnovsky 1967) Vegge et al (1971) showed that the tracer enzyme retains its size following injection into the blood stream.

Eyes from 15 rabbits and 4 monkeys (Cercopithecus aethiops) were used in this study For details concerning the doses of tracer used the exposure time to peroxidase the primary handling of the eyes and prefixation, reference is made to a previous article (Flage 1975) An essential part of the tracer technique is the ability of the

prefixation to stop the movement of peroxidase in the tissues To test the efficiency of immersion fixation in this respect fixation by perfusion was used initially in three rabbits The observations in these animals were the same as in the rest of the material 2 5 % glutaraldehyde in 0 1 M phosphate buffer pH 7 4 was used as the initial fixative both for immersion and perfusion Following prefixation and washing part of the material was cut in 20 to 40 μm sections on a freezing microtome These sections together with other thin slices of the tissues were incubated in tris HCl buffered diaminobenzidine H_2O_2 solution pH 7 6 for 30 min Some of the sections obtained on the freezing microtome were then mounted directly on slides and examined without further staining The rest of the material was postfixed in OsO_4 for 90 min, dehydrated in graded ethanols and embedded in Epon 812 1 μm sections were used for light microscopy either unstained or after staining with toluidine blue Ultrathin sections were cut on an LKB Ultrotome and examined in a Siemens Elmiskop 1A either unstained or after staining with uranylacetate and/or alkaline lead.

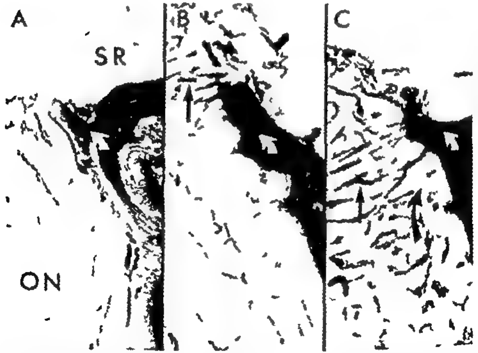

Fig 2

Comparable light microscopic sections from rabbit eyes 4 min (A) 6 min (B) and 10 min (C) after intravenous injection of peroxidase The black staining marks the tracer the sections are otherwise unstained The heavy staining of the perineural connective tissue (white arrows) the increasing staining of the intraneural connective tissue (small arrows) and the optic nerve tissue proper (arched arrow) are demonstrated Sensory retina (SR) Optic nerve (ON) × 66

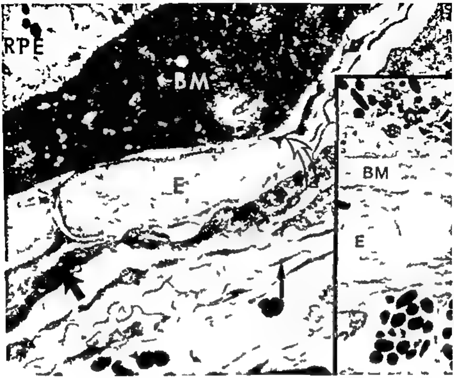

Fig 8

Perineural choroid Following intravenous administration peroxidase is present in a choroidal capillary (open arrow) staining Bruch s membrane (BM) and the extra cellular part of the choroidal connective tissue (broad arrow) The tracer is also present in the intercellular spaces in the retinal pigment epithelium (RPE) and be tween the choroidal cells (open arrow) Erythrocyte (E) Uranyl and lead × 8600 Inset The same region unstained by peroxidase × 6000

Results

The observations will be described in relation to the different tissue com ponents in the optic nerve head region (Fig 1) The terminology suggested by Hayreh (Hayreh 1972) will be used The term perineural connective tissue includes peripapillary choroid with Bruch s membrane the border tissue of Elschnig and adjacent sclera

When the differences in anatomical organization were taken into con sideration the observations made in the tissues from rabbit and monkey were in principle the same

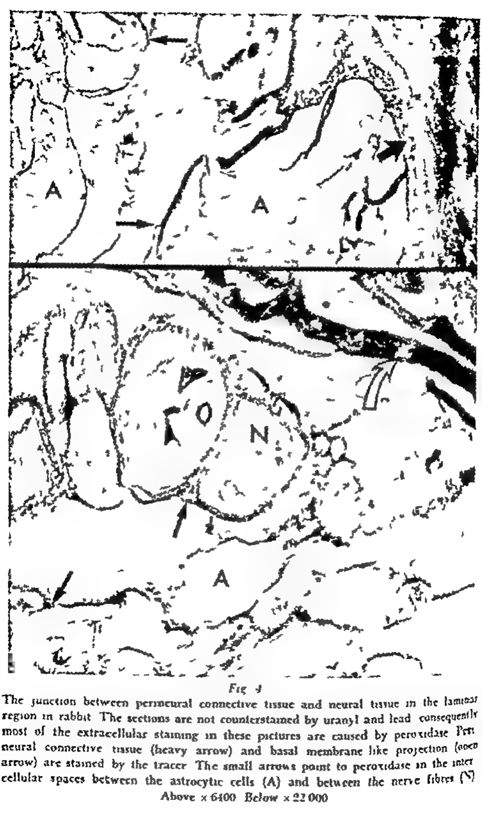

Fig 4

The junction between perineural connective tissue and neural tissue in the laminar region in rabbit The sections are not counterstained by uranyl and lead consequently most of the extracellular staining in these pictures are caused by peroxidase Peri neural connective tissue (heavy arrow) and basal membrane like projection (open arrow) are stained by the tracer The small arrows point to peroxidase in the inter cellular spaces between the astrocytic cells (A) and between the nerve fibres (N)
Above × 6400 *Below* × 22 000

Fig 3

Laminar region in monkey Peroxidase stains the connective tissue part of the lamina cribrosa (heavy arrows) The tracer is also seen in the intercellular space between two astrocytic cells (open arrow) and around the nerve fibres (small arrows) Uranyl and lead ×19 800

Within 10 min of the intravenous injection peroxidase was distributed in a distinct pattern in the tissues of the optic nerve head region (Fig 2) The tracer first appeared extravascularly in the perineural connective tissue and within a few min spread to the lamina cribrosa and intraneural perivascular connective tissue From these connective tissue components peroxidase diffused into the adjacent optic nerve tissue The details of the distribution pattern will be described under separate headings

Perineural connective tissue

The staining of these tissues was most intense in the choroid Bruch s membrane and the border tissue of *Elschnig* By means of electronmicroscopy *peroxidase was seen inside and outside the choroidal vessels staining the* intercellular spaces and the extracellular parts of the connective tissue including the scleral fibres Bruch s membrane was heavily stained (Fig 3) Anterior to Bruch s membrane the tracer entered the intercellular spaces of the retinal pigment epithelium but further diffusion into the sensory retina was *stopped* by the tight *junctions* between these cells

The junction between the perineural connective tissue and the neural tissue

The extracellular connective tissue components bordering on the nerve were stained by the tracer Basal membrane like projections heavily stained by peroxidase penetrated to varying depth into the layer of astrocytic cells inter

Fig II

Small vessel in *laminar region Peroxidase in the vessel lumen* (heavy arrow) Tight junction between two endothelial cells (open arrow) Frythrocyte (E) Lead ×60 000

Fig 7

Monkey optic nerve head region 20 min after intravenous injection of peroxidase Sensory retina (SR) retrobulbar optic nerve (ON) and subarachnoidal space (arched arrow) are unstained The neural tissue in the prelaminar laminar and retrolaminar region are stained by the tracer which also stains the perineural connective tissue the connective tissue part of the lamina cribrosa, the intraneural perivascular connective tissue and the vessels × [illegible]

intraneural connective tissue in this region consists essentially of the connective tissue part of the lamina cribrosa and the anastomosing connective tissue sheaths around the vessels (Anderson 1969) The connective tissue part of the lamina cribrosa is a continuation of the perineural scleral fibres and the majority of the small vessels in the prelaminar region and surface nerve fibre layer originate in the peripapillary choroid The perineural and intraneural connective tissue in this region are therefore closely interconnected

The final step in the development of the distribution pattern is the diffusion of the tracer from the different connective tissue components in the optic nerve head region to the adjacent neural tissue This finding demonstrates the absence of a diffusion barrier to the tracer protein between the two tissues

Following intravenous injection peroxidase does not enter the neural tissue in the intraorbital part of the optic nerve (Olsson & Kristensson 1973) This is a demonstration of the blood optic nerve barrier This barrier has two independent parts The endothelium lining the intraneural vessels make up the diffusion barrier between the blood and the neural tissue (Tsukahara et al 1973) The arachnoid membrane in the optic nerve sheaths constitutes the diffusion barrier between the nerve and the surrounding connective tissue (Nabeshima 1971) Special junctional complexes the so called tight junctions between the cells in the endothelium and in the arachnoid membrane are regarded as a necessary part of the diffusion barrier (Farquhar & Palade 1963) In the optic nerve head region the endothelial barrier of the intraneural vessels are present but the permeability barrier between the connective and neural tissues is lacking In the layer of astrocytic cells interposed between these tissues tight junctions have not been observed

The present investigation has confirmed earlier reports on a defect in the blood optic nerve barrier in the region of the optic nerve head Three observations have been found to be of particular importance in this connection 1) The high concentration of extravascular tracer in the perineural connective tissue 2) The close relationship between perineural and intraneural connective tissue and 3) The lack of a diffusion barrier between the connective tissue components and the neural tissue

The clinical importance of the defect in the blood optic nerve barrier to a protein tracer is not known It must be assumed that other large molecular substances e g proteins can enter the neural tissue in this region in the same way This may be of importance for local metabolic processes but may also predispose to pathological reactions for instance in retrobulbar neuritis

The demonstration of peroxidase between the rods and cones in the peripapillary sensory retina indicates a defect in the blood retina barrier in this

region (Cohen 1973) This observation will be a subject of further investigation (Flage 1977)

The organization of the optic nerve head region in monkey and rabbit is in some aspects different In the rabbit the nerve fibres are myelinated and the lamina cribrosa poorly developed The detailed relationship between the different tissue components are however identical in the two species The present investigation shows that the permeability properties of these tissues to a protein tracer are the same in the two species

Acknowledgment

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References

Anderson D R (1969) Ultrastructure of human and monkey lamina cribrosa and optic nerve head *Arch Ophthal (Chicago) 82* 800–814

Brightman M W Klatzo I Olsson Y & Reese T S (1970) The blood brain barrier to proteins under normal and pathological conditions *J neurol Sci 10* 215–239

Cohen A I (1973) Is there a potential defect in the blood retina barrier at the choroidal level of the optic nerve canal? *Invest Ophthal 12* 513–519

Farquhar M G & Palade G E (1963) Junctional complexes in various epithelia *J Cell Biol 17* 375–412

Flage T (1975) The distribution of intravenously administered peroxidase in the optic nerve head of rabbit and monkey *Acta ophthal (Kbh) 53* 801–808

Flage T (1977) A defect in the blood retina barrier in the peripapillary retina in preparation)

Graham [redacted] C & Karnovsky M J (1966) The early stages of absorption of injected horseradish peroxidase in the proximal tubules of mouse kidney Ultrastructural cytochemistry by a new technique *J Histochem Cytochem 14* 291–302

Grayson M C & Laties A M (1971) Ocular localization of sodium fluorescein *Arch Ophthal (Chicago) 85* 600–609

Hayreh S [redacted] (1972) Optic disc changes in glaucoma *Brit J Ophthal 56* 175–185

Karnovsky M J (1967) The ultrastructural basis of capillary permeability studied with peroxidase as a tracer *J Cell Biol 35* 213–236

Nabeshima S (1971) Morphological basis of meningeal barriers to peroxidase *Anat Rec 169* 384

Olsson Y & Kristensson K (1973) Permeability of blood vessels and connective tissue sheets in retina and optic nerve *Acta neuropath (Berl) 26* 147–156

Peyman G A Spitznas M & Straatsma B R (1971) Chorioretinal diffusion of peroxidase before and after photocoagulation *Invest Ophthal 10* 489–495

Peyman G A & Bok D (1972) Peroxidase diffusion in the normal and laser coagulated primate retina *Invest Ophthal 11* 35–45
Rodriguez Peralta L A (1966) Hematic and fluid barriers in the optic nerve *J comp Neurol 126* 109–122
Shiose Y (1970) Electron microscopic studies on blood retinal and blood aqueous barriers *Jap J Ophthal 14* 73–87
Spitznas M & Reale E (1975) Fracture faces of fenestrations and junctions of endothelial cells in human choroidal vessels *Invest Ophthal 14* 98–107
Tso M O M Shih C & McLean I W (1975) Is there a blood brain barrier at the optic nerve head? *Arch Ophthal (Chicago) 93* 815–825
Tsukahara I Miki H & Yamashita H (1975) A histochemical study on the blood optic nerve and fluid optic nerve barrier *Acta Soc ophthal jap 10* 18–3?
Vegge T Winther F O & Olsen B R (1971) Horseradish peroxidase in plasma studied by gel filtration *Histochemie 28* 16–22

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BULLOUS KERATOPATHY (FUCHS ENDOTHELIAL DYSTROPHY) TREATED SYSTEMICALLY WITH 4-TRANS AMINO CYCLOHEXANO CARBOXYLIC ACID

BY

THORKILD BRAMSEN and NIELS EHLERS

Twenty patients with bullous keratopathy (Fuchs endothelial dystrophy) were treated systemically with the antifibrinolytic drug tranexamic acid The effect was evaluated by slit lamp biomicroscopy measurement of central corneal thickness and determination of visual acuity The patients subjective complaints were also registered The duration of the treatment varied from 3 to 16 months In most cases the treatment was given over several periods with intervening free intervals
In all cases the central corneal thickness decreased and slit lamp bio microscopy revealed an improvement The visual acuity improved and all patients became free of pain
A possible mechanism involving the complement system is discussed and preliminary studies on the composition of the aqueous humour in cases of bullous keratopathy are mentioned

Key words corneal oedema – endothelium – Fuchs dystrophy – systemic treatment – fibrinolysis – complement – tranexamic acid

Fuchs endothelial dystrophy is considered as being a degenerative dystrophic disease of the cornea The condition occurs in elderly patients usually of the female sex (approx 70 % Doggart 1957) The corneal changes were first

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described by Fuchs (1910) The original material consisted of 18 elderly patients nine of whom were women Fuchs described the corneal changes as consistin of epithelial bullae and corneal oedema He was aware of the possibility that *endothelial changes might also exist but as at that time he did not possess a* slit lamp he was not able to determine this Vogt (1921) undertook slit lamp investigations of the condition and was the first to use the term cornea guttata to describe the primary endothelial changes These endothelial changes were described by him as being a deposition of fine bronze like particles on the inner surface of the cornea Stocker (1953) described six cases which commenced with an endothelial degeneration and terminated in fully developed Fuchs dystrophy – endothelial dystrophy with stromal oedema and epithelial bullae

A considerable number of histological and electron microscopical examinations of the endothelium in Fuchs dystrophy have since been undertaken (Hogan Wood & Fine 1974) In this way degenerative changes in the cytoplasm have been demonstrated together with considerable enlargement of the inter cellular spaces These intercellular spaces are filled with hyaline deposits which could conceivably be pathological secretion products of degenerated endothelial cells (Wolter & Larson 1959) Fuchs dystrophy begins in the central portion of the corneal endothelium Stromal oedema then follows which even at an early stage can be measured by pachometry Finally epithelial oedema occurs causing a marked reduction in the visual acuity and pain develops when these bullae burst

The condition requires treatment once reduction in visual acuity and pain have developed Throughout the years many different forms of treatment have been tried and most of them have proved ineffective The following forms can be mentioned osmotherapy (NaCl glucose glycerol) superficial dia or cryo thermy dry air conjunctival covering contact lenses eyelid massage warm pack pressure reducing methods steroids and thyroid stimulating methods Up to the present time the most effective method of treatment appears to be penetrating cornea transplantation

Fuchs dystrophy is a progressive disease In the literature no cases have been found where the degenerative changes have remitted In connection with an examination concerning the treatment of traumatic hyphaemas with tranexamic acid (Bramsen 1976) it was observed that the associated corneal oedema rapidly disappeared At the same time Zachariae (1975) published the results of an examination concerning the treatment of oedema in hereditary angioneurotic oedema by means of tranexamic acid It was therefore decided to undertake a clinical examination of the effect of tranexamic acid on the corneal oedema occurring in Fuchs dystrophy The condition was chosen because of its progressive nature

Material

The material consisted of 15 women and 5 men with Fuchs dystrophy The average age was 65.4 years (46–79 years) The patients were referred by ophthalmologists in the majority of cases with a view to cornea transplantation, but in a few cases the patients were referred either because of an existing cataract or because of pain.

Methods

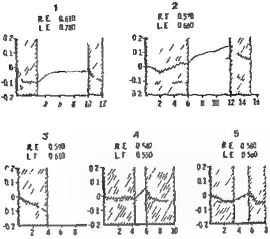
Examination before the commencement of treatment consisted of measurement of the central corneal thickness by means of a Haag Streit pachometer modified as described by Mishima & Hedbys (1968) slit lamp biomicroscopy determination of visual acuity and at the same time a subjective estimation of the pain by the patient was recorded The patients were followed up as out patients and the same examinations as described above were repeated at approximately monthly intervals The sole form of treatment was 4 trans amino cyclohexano capronic acid (Cyclokapron®) administered as tablets in a dosage of 1 g three times daily

Results

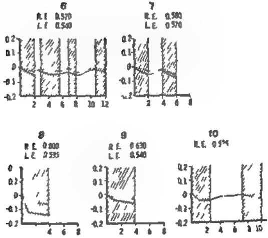
The effect of tranexamic acid on the central corneal thickness is shown in Figs 1–20 As can be seen from the graphs the period of observation varies from 3 to 16 months Intermittent treatment has been given in nine cases and therefore in these cases the patients can be considered as being their own controls

Patient No 1 was aphakic in both eyes at the commencement of treatment Patient No 2 underwent a cataract operation in the right eye after two months of treatment Patient No [illegible] underwent a corneal transplantation in the right eye after three months of treatment The disc removed from this patient was subjected to microscopical examination which revealed large areas where the endothelium was completely absent This could explain the poor effect of treatment in this patient Patient No 10 several years previously had had a conjunctival covering performed in the left eye Patient No 12 was aphakic in the left eye before commencement of treatment Patient No 19 underwent a cataract operation after four months of treatment and is included in a study concerning patients with Fuchs dystrophy and cataract operation in combination with Cyclokapron® treatment

On inspection of the graphs it can be seen that the reduction of the corneal thickness during treatment is not the same for the two eyes The thickness at the start of treatment in the two corneas is usually different and it is reasonable to suppose that an oedematous cornea can loose more water than a relatively more dehydrated one The results with regard to visual acuity slit lamp bio



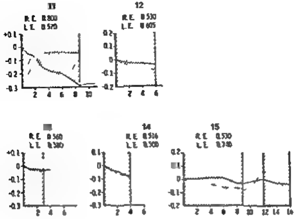
Figs 1–5



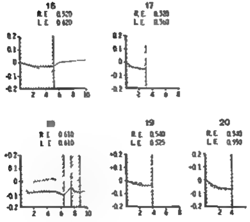
Figs 6–10

Figs 1–20

Variations in central corneal thickness during treatment with tranexamic acid Abscissa Number of months Ordinate Relative central corneal thickness in mm Hatched area Periods of treatment with tranexamic acid R E and L E Central corneal thickness before treatment Unbroken line = R E Dotted line = L E.



Figs 11–15



Figs 16–20

microscopy and pain are shown in Table I It is to be noted that on slit lamp biomicroscopy all the patients had visible endothelial dystrophy both before and after treatment In those cases where epithelial bullae are described the patients also exhibited stromal oedema

Patient no.	Age Sex	Examination before treatment: Visual acuity R.E./L.E.	Slit lamp	Pain	Examination after treatment: Visual acuity R.E./L.E.	Slit lamp	Pain
1	[illegible]	0.1 [illegible]	[illegible] b[illegible]ae		0.5 0.4	Epi[illegible]ial bullae	
		[illegible]	E[illegible]th[illegible]al [illegible]lae		light 0.2	Epit[illegible] bullae	
3	57		S[illegible] oed		0.67 0.67	St[illegible]al oedema	
4	[illegible]		Epit bullae		0.33 0.33	Epit[illegible] bullae	
		3 5	Ep[illegible] [illegible]ae		0.4 0.4	Epit[illegible] bullae	
	5		St[illegible] oe		0.8 1.0	St[illegible] oede	
			Stro[illegible] ec		0.67 0.67	S[illegible]al oed[illegible]ma	
			[illegible] llae		1 light	Epit[illegible] b[illegible]	
		0.1	Epit[illegible] [illegible]ae		0.1 0.33	Ep[illegible]al bullae	
			S[illegible] oe		1.0	Stromal oed	
11	56 ♂	0.1 0.5	E[illegible] bullae		[illegible] 1.0	[illegible]	
12	73 ♂	0.15 0.0	Epithelial bullae		0.33 light	[illegible]	
13	46 ♂	1.0 0.8	Stromal oedema		1.0 1.0	S[illegible] oedema	
14	71 ♂	0.6 0.67	Stromal oede		1.0 1.0	Stro[illegible] oedem	
15	78 ♀	0.4 light	Epithelial bullae		0.5 light	Epithe[illegible] bul[illegible]	
16	77 ♀	0.25 0.65	E[illegible]he[illegible] b[illegible]lae		[illegible] 0.2	Epithe[illegible] bu[illegible]	
17	72 ♀	0.67 1	Epith[illegible] bullae		1.0 1	Epithe[illegible]	
18	67 ♀	0.33 0.2	E[illegible]ial b[illegible]ae		0.6 0.33	Epithe[illegible] b	
19	72 ♂	0.25 0.15	Stromal oed		1 1	S[illegible]al [illegible]	
20	60 ♀	0.33 0.5	S[illegible]al oede		0.5 0.67	Stro[illegible]al [illegible]	

Table I

Visual acuity, slit lamp biomicroscopy and subjective pain sensation before and after treatment with the antifibrinolytic agent tranexamic acid

Discussion

The project is a clinical study which demonstrates that the antifibrinolytic agent tranexamic acid has an effect on the corneal oedema in Fuchs dystrophy. The mechanism of action is as yet unknown. As previously mentioned the disease occurs in elderly people although Doggart (1957) observed the condition in a 34 year old male. The disease has always been regarded as being a primary corneal disease and the progressive nature of the condition could be explained by assuming it to be a senile degeneration of the cornea. On the other hand the progressive course could also be explained if the cornea and more especially the endothelial cells were constantly exposed to cell toxic substances in the aqueous humour. The organism contains a variety of such cell toxic substances which usually occur in an inactive form, for example several of the factors in the complement system.

The mechanism by which tranexamic acid prevents the oedema from occurring in angioneurotic oedema is by means of an inhibition of the activated C_1 in the complement system. The complement system consists of factors 1–9. The classical means of activation of this system occurs when the Ca^{++} bound C_1 complex is split and forms a C_3 splitting enzyme known as C_3 convertase. This substance splits C which via complex formation with C_6 and C is able to convert a fragment of C and the whole of C_9 into a cytolytically active substance. Small defects in the cell membrane arise in this way to be

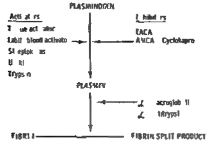


Fig 21
The fibrinolytic system

followed by passage of ions and osmotic disruption of the cell Substances present in the fibrinolytic system for example trypsin and plasmin are able to activate this complement system The antifibrinolytic substance ε amino caproic acid has an inhibitory effect on the fibrinolytic system (Fig 21) and a direct inhibitory effect on C_3 in the complement system (Soter 1975) Normal endothelial cells have no fibrinolytic activity but endothelial cells changed by degenerative processes possess such a fibrinolytic activity which increases with an increase in the degenerative processes themselves (Pandolfi & Astrup 1967)

In an attempt to throw more light on these processes we have in co operation with the blood bank Århus Kommunehospital conducted some studies on the composition of the aqueous humour with regard to the amount of α_1 anti trypsin α macroglobulin and complement factor C_3 The studies are as yet uncompleted but to date the aqueous humour from eight patients with Fuchs dystrophy has been analysed with regard to these factors Patients with cataract and normal cornea have been used as controls and 31 such patients have been analysed to date The amounts of the above mentioned factors were far higher in the patients with Fuchs dystrophy than in the control group The amount of the above mentioned substances in the primary and secondary aqueous in some cataract patients has also been analysed Values have been found in the secondary aqueous which approach those values found in patients with Fuchs dystrophy At the present time we are conducting a double blind trial to determine whether the corneal oedema following cataract operations can be influenced by tranexamic acid

The results following cornea transplantations support the supposition that it is the cell toxic substances present in the aqueous which are responsible for Fuchs dystrophy and not a primary corneal degeneration Ehlers (1974) found

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OUTFLOW OF TEARS AND ITS INFLUENCE ON TEAR SECRETION AND BREAK UP TIME (B U T)

BY

M S NORN

Schirmer s test shows that a retarded outflow of tears causes reduction of the tear secretion
The B U T is independent of the outflow of tears in patients with epiphora (119 eyes with mechanical obstruction functional obstruction or normal passage)
Mucomimetics prolong the B U T and retard the outflow of tears whereas ointments reduce both the B U T and the outflow (74 eyes)
The B U T becomes reduced when tears are absorbed by filter paper in Schirmer s test but remains uninfluenced by filter paper inserted in the fornix
The B U T is a valuable clinical test It is the resultant of many different factors (tear volume mucus fat etc)

Key words cornea – precorneal tear film – break up time – B U T – tear secretion – outflow of tears

The precorneal tear film protects the cornea against drying

Break up time (B U T) is the time elapsing from the latest blink until the occurrence of fissures in the precorneal film

A long B U T indicates a stable protective tear film A short B U T (under 10 seconds) is pathological

Read before the Danish Ophthalmological Society 26 February 1977

It is a well known fact that a reduced tear secretion involves a reduced amount of fluid in the precorneal film with a consequent shortening of the B U T. This is a typical feature of keratoconjunctivitis sicca.

We do not know how a retarded outflow of tears influences the B U T. A retarded outflow might conceivably effect a saving of fluid in the precorneal film with a resulting prolongation of the B U T. On the other hand I have shown by lacrimal river dilution test that a delayed outflow is compensated for by a reduced tear secretion (Norn 1966, 1974, confirmed by François and Neetens 1973). This reflex mechanism may perhaps normalize the B U T – or even reduce it.

The object of the present investigation has been to throw some light on the relation between B U T, outflow of tears, and tear secretion.

Material

The clinical series (A) comprises 119 eyes of 66 patients who all complained of epiphora.

The experimental series (B) comprises 74 eyes of 37 patients referred to the ophthalmic out patient department for routine examination.

Methods

Break up time

Using a stop watch, the B U T was controlled in the cobalt filtered light of the slit lamp after dying with a mixture of 0.125 % fluorescein and 0.3 % oxybuprocaine (Novesin®). Duplicate determinations were performed. (For further details see Norn 1974).

Tear secretion

This was measured using either the lacrimal river dilution test or Schirmer's test.

For the *lacrimal river dilution test* a mixture of 1 % rose bengal and 1 % fluorescein was instilled into the conjunctival sac. The lacrimal river then assumed an intense red colour. After exactly five min the dye dilution in the lacrimal river was read by comparing it with a dye dilution scale in capillary glass tubes (Norn 1966, 1974). An intense orange colour represents a 16 fold dilution. A pale yellow tinge indicates a 10.4 fold dilution.

Halberg and Berens' standardized strips were used for *Schirmer's test*. Reading was performed immediately after withdrawal and again two min later, when maximum penetration of tears into the paper had been attained.

Outflow of tears

Jones test I was employed to estimate whether there was functional passage through the lacrimal drainage system The patient was to blow one nostril at a time five and ten min after instillation for the lacrimal river dilution test Fluorescence on handkerchief in nostril or in fauces indicated spontaneous passage

In cases of failing passage washing of the lacrimal drainage system was attempted with the patient s head bent forward The wash fluid was collected in a basin and the colour recorded

If washing failed probing was performed

Result

The outflow of tears and its influence on the tear secretion is described first This is followed by reports on the influence of the *outflow* on the B U T in a clinical series (A) and the effects of vehicles on outflow of tears and B U T (series B)

Outflow of tears and tear secretion

The tear secretion was measured by Schirmer s test in two min in 32 cases The test was repeated a few min later while the lacrimal drainage system was obstructed by pressing a finger against the lacrimal sac The test was repeated again after another few min this time without compression

Table I shows that the tear secretion decreases significantly ($P < 0\,001$) in relation to obstructed outflow and normalizes again immediately after a free outflow has been regained

Table I

Tear secretion measured before during and after compression of lacrimal sac (32 tests) The Schirmer paper measured two min after withdrawal from the eye

	Before compression	During compression	After compression
Schirmer s test			
mm 2 min	7 89	3 6	8 9
SEM	0 5(	0 43	0 5ɔ
Student s *t* test	4 3	6 9	

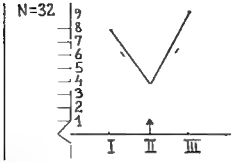

Fig 1

Influence of reduced outflow of tears on tear secretion measured by Schirmer's test Average of 32 tests measured immediately after removal of the filter paper from the eye (broken curve) and again two min later when maximum amount of fluid has been absorbed by the paper (solid curve) First test without compression second test with compression of lacrimal sac third test without compression

Ordinate Tear secretion in mm/2 min

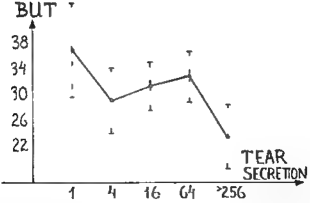

Fig 2

B U T and tear secretion of patients with epiphora

Abscissa Tear dilution/5 min measured by the lacrimal river dilution test

Ordinate B U T in seconds (duplicate determination)

Vertical bars SEM

Fig 1 illustrates the results of immediate measurement and of measurement on the same paper about two min after withdrawal from the conjunctiva

This test bore out the theory of a reduced tear secretion in relation to retarded outflow

Outflow of tears and B U T

Fig ■ shows the relation between the tear secretion of patients with epiphora (clinical series A) and the corresponding B U T measured just before the lacrimal river dilution test In such patients a reduced tear secretion must be supposed to be secondary to a retarded or totally arrested outflow

The curve suggests that a reduced outflow of tears tends to prolong the B U T However this difference is not statistically significant (Students t test) The conclusion must be drawn that in this clinical series the B U T was independent of the tear secretion

A classification of the clinical series in tear outflow groups bore out the view that the B U T is independent of the outflow conditions (Table II)

Vehicles outflow of tears and B U T

The lacrimal river dilution test was employed first for measuring the tear secretion The vehicle to be tested was then instilled from a normal eye pipette (about 50 μl) The lacrimal river dilution test was repeated a few min later

Table II

Mean B U T values in different clinical epiphora groups A total of 119 eyes (series A)

Clinical group	Definition	B U T ± SEM	Number of eyes
Mechanical obstruction	no passage on washing	35 1 ± 6 9	20
Functional obstruction	no passage of dye to nose/fauces	30 0 ± 2 7	44
Epiphora	normal passage of dye to nose/fauces	3[illegible]0 ± 3 0	56

Table III

Effects of vehicles on tear secretion and B U T Methylcellulose (MC) Polyvinyl alcohol (PVA) and simple ointment (petroleum jelly 80 % liquid paraf 20 % Ph Nord 63)

	Tear secretion		Tear reduction*	Number of eyes	*P*	B U T factor**
	before	after				
MC 0 5 %	94	49	0 8 ± 0 3	10	n s	1 36 ± 0 14 rise
MC 1 5 %	18	20	16 ± 2 0	10	< 0 002	4 36 ± 0 12 rise
PVA 1 4 %	95	87	97 ± 1 0	16	n s	1 89 ± 0 96 rise
PVA 10 0 %	217	99	1 ± 1 8	16	< 0 01	7 16 ± 0 48 rise
Simple ointment	214	159	4 2 ± 1 3	22	< 0 05	5 44 ± 0 78 fall

Ratio of tear secretions before and after introduction of vehicle calculated in the individual cases Tear reduction indicates the mean of the individual ratios (± SEM)

** From Norn & Opauszki (1977)

Mucomimetics (methylcellulose (MC) and polyvinyl alcohol (PVA) prolong the B U T thus protecting the cornea (Norn & Opauszki 1977)

In the usually employed concentrations (MC 0 5 % and PVA 1 4 %) the B U T was prolonged significantly while the tear secretion remained unchanged (Table III series B) Higher concentrations gave an additional prolongation of the B U T with a concurrent significant reduction of the tear secretion This reduction was secondary to a retarded outflow due to the viscid vehicle The patient economized on the tears a fact which may be conceived to have contributed towards the B U T prolongation

Eye ointment was seen to reduce the tear secretion significantly (Table III) presumably owing to a retarded outflow Ointment globules could be seen to partially obstruct the punctum lacrimale and the canaliculus

The B U T was found to be significantly reduced despite a retarded outflow of tears (Norn 1977) The B U T reduction was due to alteration of the lipid phase of the precorneal film

The B U T change was the reverse of that in relation to mucomimetics despite reduced tear secretion in both cases (Fig 3)

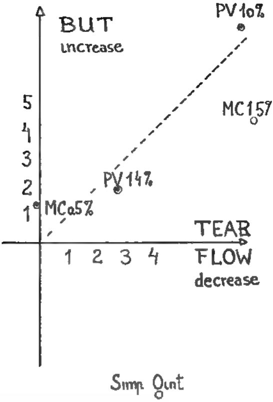

Fig 3

Effects of artificial tears and ointment on tear secretion and B U T
Abscissa Range of reductions of the tear secretion (secondary to reduced outflow)
Ordinate Range of B U T prolongations
MC = methylcellulose PVA = polyvinyl alcohol
Simp Oint = simple ointment

Experimental studies B U T

Duplicate B U T determinations were performed in 18 eyes before and during presence of Schirmer s test filter paper (Halberg & Berens) inserted at the lateral aspect of the lower lid without touching the cornea as used in Schirmer s test. The suction of tears caused a significant reduction of the B U T (2 47 ± 0 31 times average ± SEM)

A corresponding cut strip of filter paper (Halberg & Berens 5 by 5 mm) inserted laterally in the inferior fornix had no influence on the B U T (1 19 ± 0 11 times reduction 16 eyes $P < 0\ 001$ compared with the Schirmer s test experiment)

Using Schirmer's test tear fluid is removed from the eye while in the latter test experiment the tear fluid remains in the conjunctival cavity

Gelatin powder (sift 0 / mm) in the precorneal film gave no significant B U T reduction (1 34 ± 0 90 – 10 eyes) while a cut piece of egg white film on the cornea caused a significant reduction (2 19 ± 0 2 – 14 eyes) in the B U T

Discussion

The results of Schirmer's test corroborated the theory that a reduced outflow of tears causes a compensatory reduced tear secretion as demonstrated before by means of the lacrimal river dilution test The corroboration is of importance as the two tear secretion tests have different sources of error

The result was in fact surprising because we often find a broad lacrimal river in connection with an obstructed lacrimal drainage system suggesting a large volume of tears

Veirs (1976) in his book dealing with lacrimal disorders states that an apparently marked increase in tear secretion as measured by Schirmer's test may be due to obstruction of the tear drainage system The results of the above experiments militate against this view

The compensatorily reduced tear secretion is balanced in such a way that the B U T remains unaltered after reduction of the outflow On the other hand the B U T is reduced when the tears are artificially removed from the eye in Schirmer's test

B U T changes are difficult to prognosticate Many factors beyond the tear secretion must play an important role (reduced tear flow increased viscosity due to mucomimetics surface active forces of ointment irregular precorneal film in the presence of egg white film on the cornea reduced amount of mucus in A avitaminosis (Sauter 1976) damages of corneal epithelium etc)

The B U T is a unique parameter It cannot be replaced by other tests such as tests for tear secretion or outflow Despite a considerable coefficient of variation (about 30 % Norn & Opauszki 1977) it is a valuable clinical method of examination (Norn 1974)

References

François J & Neetens A (1973) Tear flow in man *Amer J Ophthal* 76 351–369
Norn M S (1966) Tear secretion in diseased eyes *Acta ophthal (Kbh)* 44 9–31
Norn M S (1974) *External Eye Methods of Examination* Scriptor Copenhagen pp 200

Contrast media currently employed in dacryocystography cause varying degrees of burning pain when instilled into the conjunctival sac, making it necessary to apply local anaesthetics prior to contrast injection The contrast medium for dacryocystography has until now consisted of one of the water soluble salts of tri iodated complex acids as diatrizoate iothalamate and others in high concentrations The use of these requires local anaesthesia

Amipaque (metrizamide) is a non ionizing tri iodated compound having only half the osmolality of conventional contrast media with the same iodide content and it is far less toxic than any of these (Holtermann 1973 Salvesen 1973 Skalpe 1973 Oftedal 1975 Evensen et al 1976 and several others)

Material and Methods

Amipaque with the same iodine concentration was first compared with Isopaque 75 % (Na Ca Mg *metrizoate*) and then with Conray Meglumine 282 (meglumine iothalamate) Two drops of each contrast medium were randomly instilled into the conjunctival sac of ten rabbits (20 eyes) and the degree of irritation was judged by the ophthalmologist who had no knowledge of which contrast medium had been instilled in each case Comparison of the same contrast media were similarly performed in double blind test on two groups each consisting of ten human volunteers

As we were convinced of the low irritating effect of Amipaque compared to the conventional contrast media double blind bilateral examinations were performed in persons with clinically normal lacrimal ducts using the same technique as described by Aakhus & Bergaust (1969) Isopaque 75 % was injected on one side and Amipaque with the same iodine content on the opposite side each patient then being his or her own control Since Isopaque causes pain conjunctival anaesthesia with Novesin 0 4 % was given to both eyes in every patient In this way the examiner could not suspect which contrast medium was being injected

Both contrast media have the same strong bitter taste

The roentgenograms of five patients in whom normal lacrimal tracts were found on both sides were carefully studied comparing the quality of demonstration of the naso lacrimal passages on both sides A second double blind series was then carried out in the same manner this time comparing Isopaque 60 % with Amipaque with the same iodine concentration and seven patients with normal lacrimal tracts were included in the study

Results

Amipaque produced only a few slow blinks in the rabbits and this was considered a normal response to the instillation procedure The two now commonly used contrast media Isopaque and Conray Meglumine however produced in every case signs of discomfort evidenced by the rapid blinking or blepharospasm which lasted about 30 seconds In all the human volunteers Isopaque and Conray Meglumine caused burning pain of short duration and moderate lacrimation and conjunctival injection was observed in practically every case Amipaque on the other hand caused no pain and only negligible conjunctival injection could be observed However one volunteer was uncertain as to whether Amipaque did cause slight discomfort

In the first series of dacryocystography examinations the common canaliculus was more clearly demonstrated with Amipaque in four cases out of five In *one case there was no discernible difference between the canaliculi* but the naso lacrimal duct was better distended on the side where Amipaque had been injected In six out of the seven cases in the second series the canaliculi and naso lacrimal duct were more clearly demonstrated on the side where Amipaque had been injected owing to the better distension with less reflux from the other punctum during contrast injection (Fig 1) There was no appreciable difference in the quality of demonstration of the ducts between the higher and lower concentrations of contrast media

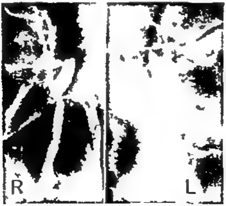

Fig 1

Dacryocystograms with injection of Amipaque 350 mg I/ml on the patient s right side and Isopaque 350 mg I/ml on the left There is better distension of the nasolacrimal passages and less reflux with Amipaque

Comments

Following Ewings report in 1909 on successful roentgenographic demonstration of two lacrimal abscess cavities and a normal lacrimal sac by injection of an emulsion of bismuth subnitrate in liquid petroleum various roentgen opaque agents have been employed in dacryocystography

Barium sulphate emulsions and oily material are not often used because barium sulphate forms concretions and may cause foreign body reaction if extravasated (Campbell 1964) Oily contrast media may cause lipid granuloma if extravasated (Eifrig 1968) and artefacts may be produced because of globule formation since the oily agents are practically non miscible with tears Such disadvantages are not seen with water soluble iodinated contrast media, which are preferred by other authors (Sargent & Ebersole 1969 Aakhus & Bergaust 1969 Putterman 1973)

We find Amipaque 350 mg I/ml to be very suitable for dacryocystography Amipaque is the only aqueous contrast medium available that does not cause

Table I

Viscosity and osmolality of some water soluble contrast media Information from the manufacturers or published values

Contrast medium	Concentration mg I/ml	Viscosity (cP)		Osmolality mol/kg 37°C
		20 C	37°C	
Conrav Meglumine 282 (meglumine iothalamate)	282	6 9	4 0	1.5
Dimer X (meglumine iocarmate)	280	13 0	[illegible] 2	1 04
Isopaque 60 % (Na Ca Mg metrizoate)	350	6 0	3 4	1 9[illegible]
Isopaque 75 % *	440	13 3	6 6	[illegible] 64
Amipaque (metrizamide)	300	12 7	6 2	0 48
	350	25 5	11 5	0.5[illegible]
	440	[illegible]0 3	25 [illegible]	0 6

* Approximate values found by extrapolation

pain when applied to the conjunctiva Its pH is about 7 0–7 6 Being non ionic the osmolality is only about one third of that of a monomer water soluble contrast medium with the same iodine content and thus approaches that of tears (Table I) An isotonic solution with iodine content of 170 mg I/ml is also available The viscosity of Amipaque is higher than both sodium and meglumine salts in the monomer form which are the media currently in use and this gives more optimal filling with distension of the naso lacrimal passages with less reflux from the opposite punctum during injection

References

Aakhus T & Bergaust B (1969) Dacryocystography in obstruction of the lacrimal passages *Acta radiol (Stockh) 8* 369–375

Bordalen B E Wang H & Holtermann H (1970) Osmotic properties of some contrast media *Invest Radiol 5* 559 565

Campbell W (1964) The radiology of the lacrimal system *Brit J Radiol 37* 1–26

Carlton W H Trueblood J H & Rossomondo R M (1973) Clinical evaluation of microscintigraphy of the lacrimal drainage apparatus *J Nucl Med 14* 89–92

Eifrig D E (1968) Lipid granuloma of the orbit *Arch Ophthal (Chicago) 79* 163–165

Evensen A Johansen J G Udnæs I & Arnesen K (1976) Orbitography with a new non ionizing water soluble contrast medium *Acta ophthal (Kbh) 54* 767 778

Ewing A E (1909) Roentgen ray demonstrations of lacrimal abscess cavity *Amer J Ophthal 26* 1–4

Holtermann H (1973) Metrizamide Introduction *Acta radiol (Stockh) Suppl 335* 1–4

Oftedal S I (1975) *Amipaque (metrizamide) A new non ionic water soluble contrast medium for the subarachnoid space* An experimental investigation in animals (Thesis) University of Oslo Press

Putterman A M (1973) Dacryocystography with occluded common canaliculus *Amer J Ophthal 76* 1010–1012

Rossomondo R M Carlton W H Trueblood J H & Thomas R P (1972) A new method of evaluating lacrimal drainage *Arch Ophthal (Chicago) 88* 523–525

Salvesen S (1973) Acute toxicity tests of metrizamide *Acta radiol (Stockh) Suppl 335* 5–13

Sargent E N & Ebersole C (1968) Dacryocystography The use of Sinografin for visualization of the nasolacrimal passages *Amer J Roentgenol 102* 831–839

Skalpe I O (1973) *Animal experimental and clinical investigations of a non ionic water soluble contrast medium (metrizamide)* (Thesis) University of Oslo Press

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Comments

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Isopaque 60 % (Na Ca Mg metrizoate)	3[illegible]0	6.0	3.4	1.9
Isopaque 75 %*	440	13.3	[illegible]6	[illegible]64
Amipaque (metrizamide)	300	12.[illegible]	6.2	0.4[illegible]
	350	2[illegible].5	11.5	0.5[illegible]
	440	70.3	2[illegible].6	0.[illegible]

* Approximate values found by extrapolation

in the anterior chamber of the eye (Dyster Aas 1965a) The mechanism of this breakdown due to α MSH is unknown but seems to differ from that of many other traumatic agents to the eye Traumata like paracentesis (Neufeld et al 1972) infrared irradiation of the iris (Bengtsson 1975) endotoxin given intra venously (Bengtsson 1975) and arachidonic acid (Podos et al 1973) given topically probably exert their damage via prostaglandin as their effects can be counteracted by acetyl salicylic acid (Aspirin®) or indomethacin which are specific prostaglandin synthetase inhibitors (Vane 1971) The α MSH effects cannot however be inhibited by these inhibitors (Neufeld et al 1972 Bengtsson 1975) and are therefore probably not mediated directly via prostaglandin synthesis and release

Imidazole a phosphodiesterase stimulating agent (Butcher & Sutherland 1962) given topically to one eye facilitates and potentiates the aqueous flare response in both the ipsi and contralateral eye induced by α MSH (Bengtsson 1976) The barrier damage due to infrared irradiation is however unaffected by topical imidazole (Bengtsson 1976) The reason why imidazole given topically to one eye affects the α MSH response in both eyes is quite obscure

It has been reported that prostaglandin E_1 (PGE_1) is accumulated by the anterior uvea more efficiently than by a number of other tissues (Bito 1972 Ehinger 1973) Furthermore this uptake has been shown to take place in the ciliary processes where the radioactive prostaglandin or its related metabolites can be detected in the stroma and vessels but not intracellularly in the epithelium or intracellularly in any other cells (Ehinger 1973) These results indicate that the ciliary epithelium perhaps has a detoxifying capacity actively transferring prostaglandin E_1 from the interior of the eye to the stroma of the ciliary processes from where it is removed by the blood stream (Bito 1974)

In our search for a possible explanation for the action of α MSH and of topical imidazole on the α MSH response we have tested whether α MSH with or without imidazole pretreatment and imidazole *per se* affect the prostaglandin E_1 accumulating capacity of the iris ciliary body For comparison we have also tested the prostaglandin uptake after stimulation with infrared irradiation of the iris which is supposed to be a prostaglandin mediated trauma

Material and Methods

Animals Adult pigmented female rabbits of mixed strains weighing between 2 5 and 4 0 kg were used They were given pellets and water *ad libitum*

Infrared irradiation Infrared irradiation of the iris was performed with the same technique as that described in a previous report (Bengtsson 1975)

Aqueous flare response The measurements of the aqueous flare in the intact eye were performed by means of a photoelectric instrument described in a previous report (Krakau & Ohman Technical note in Bengtsson 1975) The flare was measured in arbitrary units The aqueous flare increase in arbitrary units refers to the last measured value minus the baseline value

Uptake of prostaglandin E_1 The iris with the ciliary body preparation was divided into four pieces which were incubated in 8 ml of a standard Krebs Ringer bicarbonate solution After 10 min equilibration in the solution at 37 C ^3H prostaglandin E_1 100 Ci/mM (New Chemicals GmbH Dreieichenhain Germany) was added to a concentration of 1.58 ± 10^{-9} g/ml This concentration is below the physiological upper limit for prostaglandin in aqueous humour (Eakins et al 1972) and is thus not likely to affect the tissue (Bito et al 1976) Incubations were carried on for 60 min and then finally washed in non radioactive solution at 0°C for 20 min The tissue pieces (20–30 mg) were solubilized directly in Soluene (Packard Corp) and counted in a liquid scintillation spectrometer Quench corrections were obtained in conventional ways The uptake is expressed as the tissue wet weight/medium ratio (T/M)

Statistics Student s *t* test was used for calculating the significance of differences p refers to the null hypothesis (H_0)

Experiments

α MSH 20 μg/kg α MSH (freshly dissolved in 0 9 % saline) was given subcutaneously whereafter the aqueous flare was measured every half an hour for two and a half hours (Group No 2–4)

In one group of rabbits (group No 5 a) one eye was pretreated with 50 μl imidazole (freshly dissolved in saline 200 mg ml^{-1}) given topically two hours before the injection of α MSH

Regardless any aqueous flare increase was registered or not the animals were killed 2½–3 hours after the injection of α MSH i e at about the expected peak of the experimental uveitis and the uptake of prostaglandin F_1 was then determined

Infrared irradiation of the iris In two groups of rabbits one eye was treated with infrared irradiation for two min (group 9 a) and four min (group 10 a) respectively The flare response was followed for one hour and the rabbits were killed at the height of the inflammatory response The prostaglandin F_1 accumulation was then determined The contralateral untreated eye was used for control

Control groups For control the prostaglandin E_1 uptake capacity was registered in the following four groups of rabbits normal untreated rabbits (group 1) rabbits that had received 50 μl imidazole (200 mg ml⁻¹) to one eye 3 hours (group 6 a) or 24 hours (group 7 a) earlier and rabbits given imidazole intra peritoneally (group 8) (200 mg/kg body weight) 3 hours earlier

Results

The relative tritium content (T/M ± SEM) of tissue from the iris with the ciliary body and the aqueous flare increase can be seen in Table I

T bl I Th ff t f α MSH and ol nd infrared rad tio f th on th ³H PGE uptak p ty in th ir l y body f rabb t

roup no	T eat ent	Aqueous flare crease in arb ra uni Mean of maximal flare increase	Ra io re hare conten T/M m of rabbit cilia bod nc bated medio containing ³H labe prostaglandin (2 3 5)	Significance of the di erences betwe he oups
	No treatme		2 19 0 26 — 1	
2	α 5 μl	12 3 0 5	3 0 0 2 — 2	S against group 0 02 against grou 5a
3	α MS	0 50 120 2	4 02 0 — 0	0 005 ag ins group 1
	α MS	120 80 60 2 9	1 22 0 12 — 5	0 05 against group or 10 0 001 agains group 2 or 3
	Imida ole top MSH s c test eyes	10 50 8 6	3 8 0	against roup .05 against roup NS against grou 3 or 5
5b	con rol yes	0 2 3 2 4	3 52 5	NS gains roup or 2
	Imida ole 3 hour yes	—	2 56 — 6	NS against group or 7
6	ontrol eyes	—	2 29 5	
	Imidazole top 2 hours test eyes		3 6 0 — 7	p 0 025 against group
b	— con ol eyes	—	2 96 0 45	NS against group or
8	Imid zole	—	2 78 0 20 — 8	S agains group
	Infrared radiation t eyes	10 50 12 0	3 0 58	NS against group 1,2,5a,9b or 10a
9b	— control eyes	—	2 77 0 52 — 6	NS agains group
10	ared radiation test eyes	00 7 3 6 3	3 08 0 70	S against group 1 0 5 against group NS again group 0
10b	— con ol eyes		5 0 0	p 0 00 against group p 0 02 against group 9

The igure at the top of each bar represents the number of irises tested
S tands or not significant 0 5

Untreated rabbits

The mean of the physiological aqueous flare values in the group of untreated rabbits (group No 1) was 17 7 ± 3 09 (arbitrary units) and the uptake tissue/medium ratio of ^3H PGE_1 was 2 19 ± 0 26

α MSH

The α MSH treated rabbits were divided into three groups according to the induced flare values Out of 27 eyes tested 12 eyes (group No 2) turned out to be non responders i e the aqueous flare increase was less than 10 arbitrary units In 10 eyes (group No 3) there was a modest aqueous flare increase (10–50 arbitrary units) and in the remaining five eyes (group No 4) the aqueous flare response was intense (aqueous flare increase 120–180 arbitrary units) A significantly decreased prostaglandin accumulation was recorded only in the group (No 4) of α MSH treated eyes in which the aqueous flare response was pronounced On the contrary a significant increase of the uptake capacity was recorded in α MSH treated rabbits in which only a modest barrier damage (group No 3 and 5 a) was elicited whether they were pretreated with topical imidazole or not However it should be noted that in all the eyes treated with topical imidazole (group No 5 a) α MSH given subcutaneously caused a significant increase of the aqueous flare whereas no flare increase at all was seen in the contralateral untreated eyes (group No 5 b)

Topical imidazole

Topical imidazole *per se* during the first three hours after its application caused no significant increase of either the PG uptake capacity or the flare value After 24 hours however the eyes treated topically with imidazole (group No 7 a) showed a significantly higher uptake of prostaglandin compared to normal rabbits though no barrier damage was noticed In the contralateral eyes (group No 7 b) the uptake was slightly but not significantly increased

Intraperitoneal imidazole

Imidazole given intraperitoneally (group No 8) had no effect on the accumulation of prostaglandin or the aqueous flare

Infrared irradiation

To make the infrared irradiated rabbits better comparable with the groups of α MSH treated rabbits we also divided them into groups In no rabbit did

irradiation induce a flare response less than 10 arbitrary units. In six rabbits there was an aqueous flare increase between 10 and 50 arbitrary units (group No. 9 a) and in four rabbits (group No. 10 a) irradiation elicited a flare increase of 51–100 arbitrary units.

Infrared irradiation caused a slight but not significant increase of the prostaglandin uptake in both groups. In the contralateral control eyes (group No. 10 b) of the rabbits that had been irradiated for four min there was a strongly significant ($P < 0.001$) potentiation of the facilitated prostaglandin transport compared to normal rabbits. The difference against the test eyes (group No. 10 a) was not significant ($P > 0.05$) but in a paired test against their own control eyes the uptake was significantly ($P < 0.01$) decreased in 3 out of the 4 intensively irradiated test eyes.

Discussion

The present study confirms the results of Bito (1972) and Ehinger (1973) that prostaglandins (or metabolites) are accumulated in the rabbit iris ciliary body. The uptake capacity of the normal pigmented rabbits used in the present experiments is close to that found in the earlier study of Ehinger (1973) and also in the same range as that reported by Bito (1972).

Bito has shown that the active uptake of ^3H prostaglandin is blocked at the peak of experimental uveitis caused by intravitreal injection of bovine serum albumin or bacterial endotoxin (Bito 1974). Bito suggested that the active accumulation of prostaglandin under physiological conditions served as a detoxifying mechanism and that damage to this function may be an important factor in the pathogenesis of anterior uveitis (Bito 1974).

In accordance with the results of Bito (1974) we found in the present experiments that the absorptive prostaglandin transport was suppressed in the rabbit eyes in which we had recorded severe damage to the blood aqueous barrier caused by α-MSH. Judging from the morphological changes seen in the epithelium in α-MSH responders (Dyster-Aas et al. 1965b) this is hardly surprising. However, our study revealed that the prostaglandin absorptive capacity is significantly increased in the groups of rabbits in which α-MSH caused none or only moderate (aqueous flare increase < 50 arbitrary units) damage to the blood aqueous barrier. Such an increase has not previously been reported. An inflammatory reaction is consequently not necessarily always the result of a decrease in the prostaglandin uptake capacity and impairment of a hypothetical detoxifying action of the ciliary processes (as proposed by Bito (1974)) cannot be the only pathway to elicit an inflammatory response.

It was previously shown (Bengtsson 1976) that topical imidazole given to one eye facilitates and potentiates the α MSH flare in the ipsilateral eye when α MSH is injected subcutaneously 3 hours after application of imidazole and remarkably in both eyes when the interval is 24 hours. In the present study topical imidazole gave an increase in the prostaglandin absorption by the iris ciliary body after 24 hours. α MSH caused a similar increase (group No 3) as long as the damage to the uvea was not severe. It would seem that the synergistic effects of imidazole and α MSH (group No 5 a) on the aqueous flare may be related to this common action on the prostaglandin uptake although the details are still obscure. The increased uptake is by itself presumably not responsible for the aqueous flare because topical imidazole will not increase the flare although it increases the uptake.

Intraperitoneal imidazole which is known to inhibit the barrier damage caused by prostaglandin mediated agents as well as by α MSH (Bengtsson 1976) did not affect the prostaglandin uptake and probably exerts its effect via another mechanism.

Contrary to α MSH infrared irradiation causing a moderate barrier damage (aqueous flare increase of 10–50 arbitrary units) does not seem to bring about any significant change in the prostaglandin accumulating activity of the iris ciliary body. In an attempt to destroy the uptake mechanism we irradiated the iris of four rabbits for four min (instead of the usual two min) causing a pinpoint miosis and a more dense aqueous flare (mean of the maximum aqueous flare increase 736 ± 113). Not even this comparatively strong trauma destroyed the prostaglandin E_1 absorptive capacity of the ciliary body compared to normal rabbits though it caused an augmented prostaglandin accumulation in the contralateral untreated eyes. How this augmentation is elicited is obscure but further indicates that nervous reflexes are implicated in the irradiation effects which can be partly inhibited by topical anaesthetics (Dyster Aas 1965a).

Bito (1974) has shown that more intensely acting traumatic agents will cause a profound and long lasting decrease in the prostaglandin uptake. Compared to the traumatic agents used by Bito infrared irradiation is a weak trauma and explains why we could not demonstrate any damage to the prostaglandin uptake after irradiation. Our results however stress the importance of also testing more moderate stimuli as the eye seems to react differently to the same stimuli at different levels of barrier damage.

The present observation that α MSH but not infrared irradiation has an increasing effect on the prostaglandin accumulation in iris and ciliary body tissues further emphasises that α MSH exerts its damaging effect on the barrier by a mechanism which differs from that of infrared irradiation and other prostaglandin mediated stimuli.

References

Bengtsson E (1975) The inhibiting effect of indomethacin on the disruption of the blood aqueous barrier in the rabbit eye With a technical note Krakau C E T and Ohman R Measurement of the aqueous flare *Invest Ophthalmol 14* 306–312

Bengtsson E (1976) The effect of imidazole on the disruption of the blood aqueous barrier in the rabbit eye *Invest Ophthalmol 15* 315–320

Bito L Z (1972) Accumulation and apparent active transport of prostaglandins by some rabbit tissues *in vitro J Physiol (Lond) 221* 371–387

Bito L Z (1974) The effects of experimental uveitis on anterior uveal prostaglandin transport and aqueous humor composition *Invest Ophthalmol 13* 959–966

Bito L Z Davson H & Salvador E V (1976) Inhibition of *in vitro* concentrative prostaglandin accumulation by prostaglandins prostaglandin analogues and by some inhibitors of organic anion transport *J Physiol (Lond) 256* 257–271

Butcher R W & Sutherland E W (1962) Adenosine 3,5 phosphate in biological materials I Purification and properties of cyclic 3 5 nucleotide phosphodiesterase and use of this enzyme to characterize adenosine 3,5 phosphate in human urine *J biol Chem 237* 1244–1250

Dyster Aas H K (1965a) A comparison between the aqueous flare inducing effect of a α melanocyte stimulating hormone and a minimal trauma *Acta ophthal (Kbh) 43* 30–46

Dyster Aas K Ehinger B & Krakau C E T (1965b) Effect of the melanocyte stimulating hormone and of a minute trauma on the blood aqueous barrier in the rabbit eye *Acta Universitatis Lundensis* Sectio II No 20

Eakins K E Whitelocke R A F Perkins E S Bennett A & Unger W G (1972) Release of prostaglandins in ocular inflammation in the rabbit *Nature New Biol 239* 248–249

Ehinger B (1973) Localization of the uptake of prostaglandin E_1 in the eye *Exp Eye Res 17* 43–47

Neufeld A H Jampol L M & Sears M L (1972) Aspirin prevents the disruption of the blood aqueous barrier in the rabbit eye *Nature (Lond) 238* 158–159

Podos S M Becker B & Kaas M A (1973) Prostaglandin synthesis inhibition and intraocular pressure *Invest Ophthalmol 12* 426–433

Vane J R (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirinlike drugs *Nature New Biol 231* 232–235

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TIME CHANGES OF CONTRAST THRESHOLDS DURING AUTOMATIC PERIMETRY

BY

ANDERS HEIJL

Contrast thresholds were continuously recorded in six points of the visual field through a repetitive up and down staircase method using the automatic perimeter developed by Heijl & Krakau (1975b) The uninterrupted sessions lasted about 30 min Nineteen patients with a verified diagnosis of glaucoma or in whom glaucoma was suspected and twelve healthy normal subjects were tested

With increasing test time a decreased contrast sensitivity was found In most subjects the mean threshold increment was small (< 1 5 dB) The threshold increments were larger in the patient group than in the normal subjects – many test points showing increments of 6–10 dB during the test session Such a large deterioration of sensitivity was most common in eyes with visual field defects Test points which showed large threshold increments were often situated in the vicinity of documented visual field defects

In eyes with pathological visual fields the short term variation increased with increasing test time An impairment of fixation with increasing test time was found in the patient group

Key words contrast threshold – time changes – automatic perimetry – visual fields

In plotting visual fields i e determining contrast thresholds at a number of points it is often assumed generally without discussion that the probability for perception of a certain stimulus at a certain spot remains constant during

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the whole test session This point of view is practical but there are indications in literature which show that this cannot be accepted without restrictions Thus Haider & Dixon (1961) described a decrement in performance between the second and tenth minute of a continuous contrast threshold recording Ronchi and co workers described time dependent changes in visual responsiveness in a series of papers (e g Ronchi & Cetica 1972 Ronchi & Salvi 1973) Testing mainly the absolute threshold during scotopic conditions in healthy normal test subjects they found an initial drop of responsiveness during the first 40–60 min followed by cyclical sensitivity changes

Two important aims in perimetry are 1 to obtain a good reproducibility of results and 2 to detect as many pathological changes as possible in the fields investigated In conventional perimetry it is hardly possible to exercise strict control over the time conditions whereas this control is partly implicit in automatic perimetry This makes time aspects more interesting in automatic than in manual perimetry especially as an automatic computerized perimeter can without difficulty be used for time consuming test procedures like repeated threshold determinations or averaging in order to increase the reproducibility of the test results In discussions of test logics for automatic perimetry a stationarity of contrast thresholds at least for a limited period of time has often been assumed (Fankhauser Koch & Roulier 1972 Heijl & Krakau 1975a Spahr 1975 Bebie Fankhauser & Spahr 1976) We have had the impression that this assumption could be wrong (Heijl & Krakau 1975a b Heijl 1976) and preferred short test sessions for automatic perimetry Is the assumption of stationarity well founded or is there a risk of changed thresholds if testing is continued over long periods?

The aim of this paper is to investigate whether important time changes of contrast thresholds appear in automatic perimetry and whether there are differences in this respect between patients and healthy normal test subjects

Material

Two groups of test subjects were used

1 Twelve healthy normal test subjects six were young (< 30 years) – mean age 24 years six were older (≥ 45 years) – mean age 54 years

2 Nineteen patients (mean age 68 years) All patients either had a verified diagnosis of glaucoma or glaucoma was suspected (raised intraocular pressure cupped discs) In eleven of the eyes tested there were visual field defects

The patients thus constituted a fairly representative selection who because

of a definite diagnosis of glaucoma or because of suspected glaucoma must be subjected to perimetry

Most healthy normal subjects had very little experience of perimetry The patients had been examined with the Goldmann perimeter but their experience of automatic perimetry was limited

Only one eye was tested in each subject

Methods

A fully automatic computerized perimeter developed by Heijl & Krakau (Heijl & Krakau 1975b) was used This is a perimeter with 64 static stimuli (light emitting diodes) covering the central visual field The stimuli can be exposed on 16 intensity levels The ratio between two consecutive levels is 1 2

The specifications of the *computer test logic* used were

a Only six out of the 64 test points of the perimeter were used but these points were repeatedly tested Two of these points were situated at 5° of eccentricity two at 10° and two at 15°

b Another stimulus was exposed in the patient s blind spot area at random intervals This served as an indicator of the patient s fixation Obviously if the patient kept his fixation correctly this light could not be seen

c The contrast threshold was determined by a repetitive up and down staircase method (Fig 1) If a test point l was illuminated at an intensity i and the patient perceived the light and pressed the answering button the light intensity of this l th point the next time it was chosen was at a one step fainter level (called *i + 1*) If on the other hand the test light was not perceived its intensity would next time be one step higher (level *i – 1*) This process was repeated during the whole test and it can be regarded as a Markov process with reflecting barriers (compare Heijl & Krakau 1975a) If the frequency of seeing curve of the retinal point tested is constant the process will stay inside a certain number of levels during the whole test and a curve of the intensity levels visited (i e the intensity levels exposed) (Fig 1) will show no long term trend

d The test session was divided into twelve periods In each of these periods a stimulus was presented ten times in each of the six test points and in the blind spot area Thus each period of the test contained 70 stimulus presentations and a full test session contained 840 stimulus presentations The order in which the stimuli were shown within each period was randomized Stimulus exposure

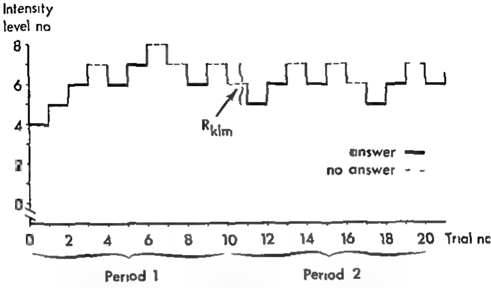


Fig 1

Example of test procedure at one single test point Stimulus intensity level number increases (i e stimulus intensity decreases) with every answer from the patient (thick horizontal lines) and decreases when no answer is given (broken horizontal lines) R_{klm} is the range of the stimulus intensity levels visited during one test period

time was 0 5 s and interstimulus interval 2 0 s if the patient did not react to the stimulus by pressing his button In case of an answer from the patient a new stimulus was presented 0 5 s after this answer

Statistical Methods

For each test subject (k) each test point (l) and each period of the test (m) the mean (M_{klm}) of the stimulus intensity levels visited was calculated

Similarly the ranges (differences between the highest stimulus intensity level and the lowest stimulus intensity level) R_{klm} for each subject test point and period were stored by the computer during the test

In order to investigate whether or not there was stationarity during the test linear regression analyses versus test period were carried out on the means of the levels visited (M_{klm}) and on the ranges (R_{klm}) – one analysis for each test point in each patient Thus these analyses were performed with the values of k and l kept constant for each analysis but with variation of the m value from 2 to 12 (The M_{klm} and R_{klm} values from the first test period of the sessions were not used since a number of stimulus presentations is usually needed before the patient reaches his threshold zone)

As no obvious cyclical or other specific components could be seen in the threshold curves we consider linear regression analysis to be justified and proper for the purpose of investigating the long term trend of the test

The regression analyses resulted in a number of regression coefficients (called C^M_{kl} for the means of the exposed intensity levels and C^R_{kl} for the ranges) plus the variances around the lines of regression A regression coefficient $C^M_{kl} = -0.050$ thus meant that the means of the levels visited showed a tendency to decrease during the test the decrement corresponding to half an intensity level unit between the second and the twelfth period of the test

The following statistical treatment was then carried out

Mean thresholds For each subject the mean of the regression coefficients of the mean threshold was calculated Usually the C^M_{kl} values from all the six test points were used in this calculation

$$C^M_k = \frac{1}{6} \sum_{l=1}^{l=6} C^M_{kl}$$

However test points where the means of the levels visited were *constantly* ≤ 1 *were* omitted Such test points were considered to be situated in a scotoma As the maximum stimulus intensities of the perimeter were used at these points a further decrement of sensitivity could not be measured and a regression coefficient (C^M_{kl}) would falsely be close to zero Using the variances of the lines of regression the 95 % confidence limits of the mean slope of each subject (C^M_k) were calculated If both 95 % confidence limits of the mean slope carried a negative sign a threshold increment with increasing test time was established on the 5 % significance level

The sign test was performed on the C^M_k values of the two groups of test subjects (normals and patients) in order to investigate whether there was a general *significant* time dependent threshold change in either of these groups

A comparison between more central (5°) and more peripheral (15°) test points was made For each subject the mean of the threshold slopes (C^M_{kl}) for the 15° points was subtracted from the mean of these slopes for the 5° points The sign test was used on these differences

Ranges The mean of the regression coefficients for the ranges was calculated for each test subject

$$C^M_k = \frac{1}{6} \sum_{l=1}^{l=6} C^R_{kl}$$

In this calculation all test points were omitted whenever the means of the levels exposed (M_{klm}) at any time during the test were close to 0 or 1 In such circumstances it cannot be expected that the patient's true threshold variation is measured

The sign test was then applied to the mean regression coefficients (C^R_k) in the same manner as with the C^M_k

Fixation The patients answers on blind spot stimulus presentations were stored by the computer during the test The ratio between answers and presentations constituted the fixation index There was one fixation index (F_{km}) for each period of the test (m) in each test subject (k)

The statistical treatment of these indices were carried out in two different ways

a The indices were summed for the first six and for the last six test periods respectively for each test subject The second of these sums was subtracted from the first

$$\sum_{m=1}^{m=6} F_{km} - \sum_{m=7}^{m=12} F_{km}$$

If this difference was < 0 there were more (false) answers on blind spot stimulus presentations during the second half of the test than during the first

b For each subject linear regression analyses of the indices (F_{km}) were performed The sign test was then applied to the coefficients of regression exactly as was done with the mean intensity level slopes

The correlation if any between the mean fixation index of each subject ($F_k = \frac{1}{12}$

$$\sum_{m=1}^{m=12} F_{km}$$) and the mean stimulus range ($R_k = \frac{1}{66} \sum_{m=2}^{m=12} \sum_{l=1}^{l=6} R_{klm}$) of each subject was tested with Spearman s rank correlation test

Experiment

The test situation for the patients and the normal subjects was exactly the same as in our routine automatic perimetry (Heijl 1976) Before the test was started the blind spot stimulus was so adjusted as to fall in the blind spot area of the eye to be tested The subject was instructed to keep his gaze steady on the fixation spot and to press his answering button when a stimulus was perceived The subjects were not informed of the purpose of the test but knew the approximate expected test time

The experiments were carried out at a background luminance of 1 0 or 0 1 cd/m All the subjects were corrected for ametropia and for near vision The test duration was measured

Results

The duration of the test session was found to range between 24 67 and 32 48 min. The mean duration was 28 17 min The difference in mean duration between patients and normals was small (1 31 min)

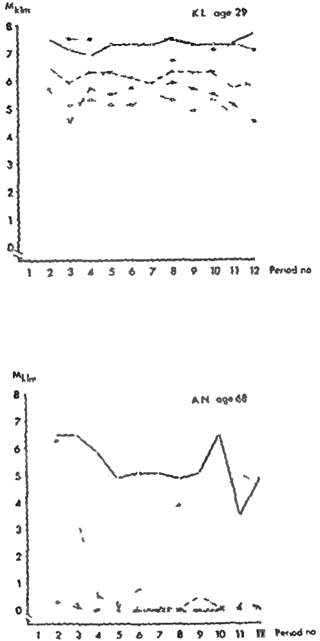
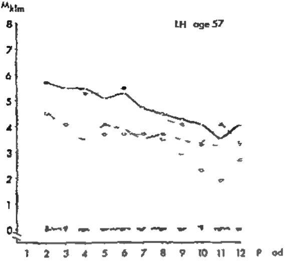


Fig. 2 A–B

Time changes of the means of the intensity levels visited during each test period (M_{kl}). Each graph contains the results from all the six points tested in each subject.
a. Normal test subject. M_{klm} values remain fairly constant.

b. Patient with visual field defects. Two test points are situated in a scotoma. Two test points show large threshold increments.



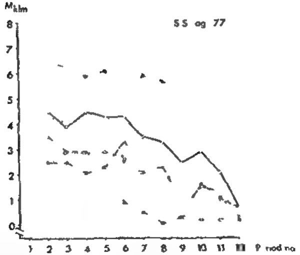


Fig 2 C–D

c Patient with visual field defects Two tes points are situated in a scotoma The remaining four test points all show similar threshold increments

d Patient in whom no visual field defects were documented at the time when the above registration was obtained although the disc showed large cupping One year after this registration was made the patient had developed visual field defects in this eye Pronoun ed time changes at most points Thresholds remain at fairly constant levels during the *first test periods*

Long term threshold variation The means of the intensity levels exposed (M_{klm}) which reflect the thresholds during the different periods of the test were found to vary considerably (compare Fig 2)

For the group of *normal test subjects* the mean of the regression coefficients (C^M) was found to be small (mean slope −0 028) In every test subject the mean of the slopes (C^M_k) however carried a negative sign For six of the twelve mean slopes both 95 % confidence limits were negative which shows that in these cases the time dependent increment in threshold was statistically significant at the 5 % level The general effect of time on threshold in this group was however small (compare Fig 2 a)

In the *patient group* a larger long term threshold deterioration with time was found In *the eyes with normal visual fields* (eight eyes) the mean slope was −0 061 Four of these eyes showed a significant negative mean slope (at the 5 % significance level) one of which had a steep mean slope (−0 28) On the other hand one of these eyes demonstrated a positive mean slope Among *the eyes with pathological visual fields* (eleven eyes) the mean slope was somewhat steeper (−0 105) and all the mean slopes carried a negative sign Furthermore all except one of these pathological eyes had a significant negative mean slope at the 5 % significance level There were several patients in this group who showed fairly high mean slopes (e g five mean slopes < -0 1) and there were more than a dozen test points where the threshold showed an increase of more than two intensity steps ($\approx$ 6 dB) during the test in the patient group

Further it was found that there was a clear positive correlation between the slope of the test points and the proximity of the test points to visual field defects so that test points with steep slopes were often situated in the vicinity of documented visual field defects

With the sign test a significant time dependent threshold deterioration could be established in the *patient group* ($P < 0$ 1 %) and in the *group of normals* ($P < 1$ %) In most eyes where a large deterioration with increasing test time was found it was noticed that much of the impairment took place during the later part of the test while thresholds were fairly close to the initial level during the first few periods of the test (4–10 min or so) (compare Figs 2 b 2 c and 2 d) In the group of normal test subjects as well as in the patient group no significant difference in long term threshold changes could be found between more central (5) and more peripheral (15°) test points

Ranges The threshold ranges from the different periods mirror the short term variation during the test (Each period takes about 2 5 min) With the statistical methods described no significant trend towards increasing or decreasing ranges with increasing test time could be established either in the group of normal

subjects or in the patient group. If the group of *eyes with pathological visual fields* was treated in isolation it could be established at the 5 % significance level that an increase of the ranges took place in those eyes during the test. The mean range impairment was rather small however, amounting to about *0.5 stimulus intensity step* ($\approx$ *1.5 dB) between the second and the twelfth* periods of the test.

When the 95 % confidence limits of the mean slopes of the ranges were calculated it was found that no subject showed a statistically significant decrement of the range with increasing test time, while four patients and one normal test subject showed statistically significant increments of the ranges with time.

Fixation. Both procedures a and b (see "Statistical Methods") demonstrated that in the *patient group* there was a statistically significant impairment of the fixation index (F_{km}) during the test ($P < 5$ %) while no significant influence of an increased test time on the fixation index could be shown in the group of *normal subjects*. There were 50 % more (false) answers on blind spot stimulus exposure during the second half of the test than during the first.

As might be expected, a positive correlation could be established between fixation indices (F_k) and stimulus intensity ranges (R_k) ($P < 0.1$ %) in the patient group. In the group of normal subjects this was more doubtful (5 % $< P <$ 10 %).

Discussion

It is obvious from the results that most subjects, normal as well as patients, exhibit an increased contrast threshold, i. e. a decreased contrast sensitivity during one test session. In the normal group and in most of the patients this decrement was fairly small, often corresponding to an impairment in sensitivity of roughly half a stimulus level step (i. e. $\approx$ 1.5 dB) or less during the whole test session (Fig. 2 a). Such a small change is negligible from a practical point of view.

However, some subjects showed a remarkable and very important decrement in contrast sensitivity during the test session (compare Figs. 2 b and 2 d). This phenomenon was fairly common and could show threshold increments exceeding 10 dB during the test. The curve of the mean levels visited (M_{klm}) during the different test periods was sometimes so steep that the regression coefficient calculated over the periods 2–12 (C^M_{kl}) did not show the full extent of the impairment (compare Fig. 2 b). Large threshold increments with increasing test time were observed almost exclusively in the patient group and were most prevalent in the group of eyes with pathological visual fields.

It might be objected that as the patient group had a higher mean age than the group of older normal subjects this difference in time dependent threshold impairment could be explained by the age difference alone However when five of the youngest patients with visual field defects were selected in order to form a group where the mean age matched the mean age of the four oldest subjects in the group of older normals no single test point showed a large threshold increment ($C^{M}_{kl} < -0.1$) in the normal group whereas in the matched patient group there were nine points with a $C^{M}_{kl} < -0.1$ Thus a clear difference remained even if groups with similar age distributions were compared

Among the eyes with visual field defects there was also a statistically significant increase in the range of visited intensity levels an increase in short term variation with increasing test time

The fixation index showed a significant time dependent deterioration in the patient group This could have two different causes 1 There was an impairment of the patients fixation during the test 2 The false positives (patients pushing the answering button when no stimuli were present) increased generally during the test However the latter explanation seems somewhat far fetched since a general increased frequency of false positives would have yielded an effect on visited intensity levels opposite to the one observed in this study Furthermore in a similar experimental set up an automatic adaptometer we have noted that false positives are infrequent (compare Heijl & Krakau 1975a) Thus it seems more resonable to assume that the increment in fixation index is due to a time dependent impairment of the patients fixation capability

We have deliberately preferred the test situation described – a continuous test Thus the phenomena mentioned appear in such a test We do not maintain that identical changes appear in a test situation with interruptions whether these are induced by the patient the computer or the examiner

In perimetry our aim is twofold 1 reproducibility and 2 sensitivity in detection of visual field defects If stationarity had existed the situation would have been simple It would have been possible to attain almost any high degree of precision by using very long test sessions with the calculation of the mean of repeated threshold measurements or similar procedures As the assumption of a steady state must now be largely rejected two somewhat different attitudes could be taken

1 If we assume the primary aim of perimetry to be maximal reproducibility the time changes constitute a disadvantage which must be taken into consideration in for instance the construction of test programmes for automatic perimetry As there are not only test sessions where all test points show fairly similar time changes (Fig 2 c) but also sessions where the increment of the

threshold with time is much more pronounced in some test points than in others (Figs 2 b and 2 d) the time induced changes will lead not only to a general constriction of the visual field when the test is prolonged but also to variations in the form of the visual field There is a possibility that a steady state could be reached after prolonged testing but there is no indication from the results of this study that such a state is attained during the first half hour of the test As we do not know whether similar time changes appear in repeated measurements prolonged tests might very well also lead to impaired reproducibility even when the duration of the test session is kept constant There may be cases in whom better reproducibility could be obtained by a crude test completed in 4–10 min when the threshold deterioration usually remains modest, than by a time consuming refined test even if the long term threshold changes in most subjects are so small that an averaging procedure should be favourable

2 If instead we assume that the primary aim of perimetry is to find as many visual field abnormalities as possible another point of view could be taken By continually exposing stimuli automatic perimetry can be made to put a strain on the patient maybe acting as a provocative test. The fatiguability demonstrated during a long test might reflect a functional loss – early developing visual field defects or enhancements of existing defects This phenomenon might be related to the fatigue like effect reported by Enoch and co-workers (Sunga & Enoch 1970 Enoch et al 1970 Enoch & Lawrence 1975) However this fatigue like effect is attributed to lesions central to the optic disc and it was not seen in glaucoma The hypothesis of the threshold impairment representing a functional loss is supported by the spatial correlation found between points showing large sensitivity decrements and existing visual field defects Thus this time dependent sensitivity impairment might be an asset and not only a drawback – the deterioration in itself might help us to discover early pathological changes

We have noticed earlier that visual field defects often seem to be exaggerated with automatic perimetry as compared to manual perimetry (Heijl & Krakau 1975b) and such an enhancement has also been seen by Fankhauser (1976) at a later date This increased sensitivity of automatic perimetry may at least partially be explained by the time dependent threshold deterioration described

The results differed largely between the patient group and the normal subjects in this study the time changes were much more pronounced in the patient group Thus the conclusion can be drawn that test logics for automatic perimetry should not be tested on a material of normal subjects only but also on patients

References

Bebie H, Fankhauser F & Spahr J (1976) Static perimetry: Accuracy and fluctuations. *Acta ophthal (Kbh)* 54 339–348
Enoch J M, Berger R & Birns R (1970) A static perimetric technique believed to test receptive field properties: extension and verification of the analysis. *Docum ophthal* 29 127–153
Enoch J M & Lawrence B (1975) A perimetric technique believed to test receptive field properties: sequential evaluation in glaucoma and other conditions. *Amer J Ophthal* 80 734–758
Fankhauser F (1976) Personal communication
Fankhauser F, Koch P & Roulier A (1972) On automation of perimetry. *Albrecht v Graefes Arch Ophthal* 184 126–150
Haider M & Dixon F (1961) Influences of training and fatigue on the continuous recording of a visual differential threshold. *Brit J Psychol* 52 227–237
Heijl A (1976) Automatic perimetry in glaucoma visual field screening. A clinical study. *Albrecht v Graefes Arch Ophthal* 200 21–37
Heijl A & Krakau C E T (1975a) An automatic static perimeter: design and pilot study. *Acta ophthal (Kbh)* 53 293–310
Heijl A & Krakau C E T (1975b) An automatic perimeter for glaucoma visual field screening and control. Construction and clinical cases. *Albrecht v Graefes Arch Ophthal* 197 13–23
Ronchi L & Cetica M (1972) Time changes of absolute threshold luminance across a 2 hour lasting uninterrupted session. *Atti Fond G Ronchi* 27 937–958
Ronchi L & Salvi G (1973) Time changes of absolute threshold luminance across the visual field. *Ophthal Res* 5 113–120
Spahr J (1975) Optimization of the presentation pattern in automated static perimetry. *Vision Res* 15 1275–1281
Sunga R N & Enoch J M (1970) Further perimetric analysis of patients with lesions of the visual pathways. *Amer J Ophthal* 70 403–422

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EFFECT ON INTRAOCULAR PRESSURE OF RETROBULBAR INJECTION OF XYLOCAINE WITH AND WITHOUT ADRENALINE

BY

MAGNUS GJÖTTERBERG and SVEN OLOF INGEMANSSON

The changes in IOP were registered in two groups each comprising 50 patients after a retrobulbar injection of Xylocaine and Xylocaine adrenaline respectively No significant difference between the mean values of the initial pressures and the IOP during the following ten min could be proved in either of the groups but in several individual cases there was a considerable and unpredictable change in IOP following the injection After ten min this effect was still often present but less pronounced The change in IOP was significantly greater when adrenaline was used As a result of these findings the authors have been inclined to cease using adrenaline in retrobulbar anaesthesia for intraocular surgery of short duration

Key words adrenaline – epinephrine – intraocular pressure – lidocaine – retrobulbar anaesthesia – vitreous loss

In intraocular surgery it is considered advantageous if the intraocular pressure (IOP) is low when the eye is being operated upon However opinions differ regarding the type of complication that a raised IOP might cause For a long time it was generally considered that in cataract surgery a high IOP would increase the risk of vitreous loss because of a high vitreous pressure per se (Elschnig 1927 Iliff 1966) This has been questioned by several authors (Miklos

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& Halmai 1964 Kettesy 1967) They believe that vitreous loss is usually caus by the extraocular muscles pressing on the globe Nowadays there is gener agreement that this is the major cause of vitreous loss which however ma also be caused by other mechanisms When the eye is opened the IOP suddenly reduced to that of the atmosphere If the initial pressure is elevate the high pressure gradient so created will cause great stress on the intraocul vascular tree increasing the risk of haemorrhage at worst of the expulsive typ (Taylor 1974) Taylor favours the opinion that there are many vascular blow outs of small magnitude leading to sudden loss of vitreous The bleeding vess is tamponaded by closure of the eye

As regards reducing IOP prior to intraocular surgery retrobulbar anaesthesi among several other methods has been considered effective Elschnig (192 meant that a retrobulbar injection (RBI) of procaine caused a considerabl reduction in IOP in the course of eight to ten min Atkinson (1934) and Giffor (1949) obtained similar results On the other hand Miklos & Halmai (196 registered a reduction of IOP not greater than 11 per cent The compositio of the local injection used by the above mentioned authors varied and it i possible that addition of adrenaline (epinephrine) might lower IOP over an above the effect of the anaesthetics used (Atkinson 1934) Gifford (1949) an Miklos & Halmai (1964) studied this but their results do not permit any definit conclusions to be drawn

In all the above discussed investigations IOP was measured with the Schiot tonometer Applanation tonometry is a more reliable method The introductio of hand held applanation tonometers (Draeger 1967) created the opportunit to perform applanation tonometry on the supine patient as well In the ligh of these facts we decided to measure by means of applanation tonometry th change in IOP after RBI of Xylocaine (lidocaine) and Xylocaine adrenalin respectively

Material and Methods

The material consists of 60 patients with an average age of 71 years and ranging from 30 to 92 years 58 of these patients underwent cataract extraction one an operation for retinal detachment and another was treated with cryopexy for a retinal rupture

Patients suffering from glaucoma and patients previously affected by ocular diseases known to cause changes in the IOP were excluded

The patients were divided into two equal groups consisting of patients with even and uneven dates of births respectively The former group was given an injection containing 2 ml of Xylocaine (lidocaine 20 mg/ml) without any

supplement the latter 2 ml of Xylocaine with adrenaline (20 mg/ml and 12.5 μg/ml).

The patients were given the premedication administered at the hospital to all patients prior to cataract surgery. Thus each patient below the age of 70 was given 10 mg of diazepam orally on the evening prior to surgery and 15 mg of diazepam one h before undergoing surgery. Patients over the age of 70 were given 5 and 10 mg respectively.

The orbicularis muscle was paralysed ad modum van Lindt. The RBI was given in the muscle cone with a 3.5 cm needle in accordance with the instructions published by Atkinson (1934).

The IOP was measured in the operating theatre before the injections were administered and subsequently after one, two, five and ten min. For superficial anaesthesia we used 2 drops of tetracaine and for dyeing purposes fluorescein was used. The IOP was measured ad modum Draeger with a handheld ap

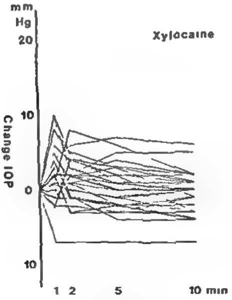

Fig. 1

Group A. Changes in IOP of 30 patients after a RBI of 2 ml of *Xylocaine (20 mg/ml)*. The initial pressures are shown as being equivalent to zero. The ordinate indicates changes in IOP and the abscissa the points of time when IOP was measured. The values of the individual patients have been connected. Some of the lines coincide and give an impression of a somewhat coarser line.

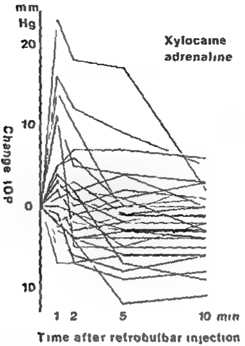

Fig 2

Group B Changes in IOP of 30 patients after RBI of 2 ml of Xylocaine with adrenaline (20 mg/ml and 12.5 μg/ml) The initial pressures are shown as being equivalent to zero The ordinate indicates changes in IOP and the abscissa the points of time when IOP was measured The values of the individual patients have been connected

planation tonometer For technical reasons the IOP was registered with readings confined to the nearest millimeter marking

Moses (1961) and Bechrakis (1966) have noticed that IOP decreases by a few mm of Hg following repeated applanation tonometry The mechanism behind this change in IOP is unknown In our investigation it has been difficult to evaluate the effect of repeated applanation tonometry and we have not been able to consider this factor in our compilation However a decrease in IOP via this mechanism should prove equal in both groups

Results

The mean value of the IOP before RBI was 17 1 mmHg in the group that received Xylocaine only (group A) and 18 9 mmHg in the group that received Xylocaine with adrenaline (group B)

Figs 1 and 2 show the changes in IOP in the individual patients in group A

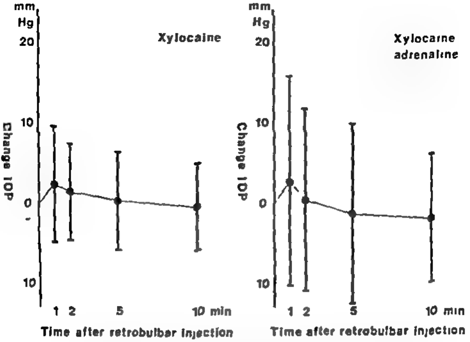

Fig 3

The mean value of the changes in IOP of 30 patients after a RBI of 2 ml of Xylocaine (20 mg/ml) and of 30 patients after a RBI of Xylocaine with adrenaline (20 mg/ml and 12.5 μg/ml) The vertical lines represent $\pm 2\times$ the standard deviation. There is a significant greater dispersion ($P < 0.05$) of the values in the group that received Xylocaine with adrenaline

and B respectively In group A there was generally a slight increase in IOP after the injections At the reading after two five and ten min this rise as a rule decreased and approached the initial values In group B there were approximately the same conditions but it appears from the figures that there was a considerably greater dispersion of the values in this group

Fig 3 shows the mean values of the changes in IOP and two times the standard deviation at each reading in the two groups In group A the mean value increased after one min and then decreased After five min the mean value was near zero and after ten minutes 0 5 mmHg below zero In group B as well as in group A the mean value increased after one min but after two five and ten min there was a more obvious fall The mean value after ten min was 1 8 mmHg below zero There is no statistically significant difference between the corresponding values of the two groups when calculated with a

Besides when adrenaline was omitted we did not notice any reduction of the depth of anaesthesia nor were any other disadvantages such as increased bleeding observed Also in the case of the elderly patient adrenaline may have systemic effects which are not to be desired

References

Atkinson W ▮ (1934) Local Anesthesia in Ophthalmology *Trans Amer ophthal Soc 32* 399–451

Bechrakis E (1966) Über den spontanen Druckabfall bei Applanationstonometrie *Ophthalmologica 151* 604–614

Colle J Duke Elder P M & Duke Elder W S (1931) Studies on the intraocular pressure Part I The action of drugs on the vascular and muscular factors controlling the intra ocular pressure *J Physiol (Lond) 71* 1–30

Draeger J (1967) Principle and clinical application of a portable applanation tonometer *Invest Ophthal 6* 132–134

Elschnig A (1927) cited by Miklos & Halmai (1964)

Gartner S (1959) Methods of inducing anesthesia and hypotony for cataract surgery *Arch Ophthal (Chicago) 61* 50–51

Gifford H (1949) A Study of the Effect of Retrobulbar Anesthesia on the Ocular Tension and the Vitreous Pressure *Amer J Ophthal 32* 1359–1368

Iliff C E (1966) A surgically soft eye by posterior sclerotomy *Amer J Ophthal 61* 2/6–?/8

Kettesy A (1967) Glaskorperverlust Haufigkeit Bedeutung Ursachen und Verhutung *Klin Mbl Augenheilk 150* 785–804

Miklos A & Halmai O (1964) Verringert retrobulbare Injection oder digitale Kompression die Haufigkeit des Glaskorperverlustes bei Staroperationen? *Klin Mbl Augenheilk 144* 92–115

Moses R A (1961) Repeated Applanation Tonometry *Ophthalmologica 14?* 663–665

Taylor D M (1974) Expulsive haemorrhage *Amer J Ophthal 78* 961–966

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APHAKIC GLAUCOMA

BY

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In a successive cataract series of 874 eyes which underwent operation for senile cataract by microsurgery and had no preoperative diagnosis of glaucoma 16 (1 8 %) were found to have aphakic glaucoma after a follow up period ranging from 10 months to 6 years

Of these cases 44 % (7 eyes) had pupillary block 37 % (6 eyes) canal block and 19 % (3 eyes) angle block without primary pupillary block whereas no eye showed ciliary block

The cause of pupillary block in the present series appears to have been the use of iridotomy instead of iridectomy (in 6 of the 7 cases) In 5 of the 7 cases with pupillary block the manifest aphakic pupillary block had been preceded by increasing vitreous herniation into the pupil without rupture of the hyaloid membrane This situation designated relative aphakic pupillary block is assumed to precede in most cases the manifest aphakic pupillary block and is therefore of diagnostic importance, unlike stationary vitreous hernia In the group with canal block the mean preoperative ocular tension had been higher than in the other groups When considering also the normal postoperative gonioscopy this makes us interpret these cases as latent simple glaucoma (canal block) rendered manifest by the cataract operation

This small series does not afford any indication to assume that a corneal cataract incision involves less risk than a corneo scleral incision of injuring Schlemm s canal

Treatment was predominantly surgical in the group of pupillary block predominantly medical in the others

Key words aphakic glaucoma – aphakic pupillary block – aphakic canal block – aphakic angle block.

The object of this study was to investigate the occurrence of aphakic glaucoma in a successive material of eyes that had undergone microsurgery for senile cataract

Aphakic glaucoma is taken to mean the co existence of aphakia and glaucoma without a diagnosis of the glaucoma having been made preoperatively

Another object was to try classifying the aphakic glaucomas aetiologically

Material and Method

The material consists of patients who had cataract operations by a micro surgical technique during the period 1970–76 in the University Eye Clinic Rigshospitalet Copenhagen Cataract operations using a corneal incision and continuous nylon sutures were carried out to a major extent only during the period 1975–76 Otherwise the technique was a corneo scleral incision with a conjunctival flap and knotted sutures The number of iridectomies and iridotomies in the material must be assumed to be approximately the same as there were no fixed lines in this respect during the study period

For each patient a discharge card was sent to the referring ophthalmologist who then investigated in his files whether postoperative ambulatory follow up and shown any signs of aphakic glaucoma Our cataract material comprises 615 patients or a total of 874 eyes The follow up period ranges from 10 months to 6 years As already mentioned eyes in which a diagnosis of glaucoma had been made preoperatively were not included in the analysis Nor were eyes with a history of corneal transplantation and retinal detachment or eyes in which an intraocular lens was used The 615 patients make up 66 % of those who underwent cataract surgery during the study period

For the patients found to have aphakic glaucoma the case records were perused with a view to 15 items concerning each eye viz

Preoperative tension operative vitreous loss iridectomy/iridotomy postoperative depth of chamber (1st postoperative week) increasing vitreous herniation into the pupil postoperatively goniosynechiae postoperatively postoperative uveitis corneo scleral cataract incision/corneal incision postoperative chamber haemorrhage capsular rupture use of chymotrypsin epithelization diabetes pseudoexfoliation treatment (medical and/or surgical)

On the basis of this registration we tried to classify the material into cases of pupillary block cases of angle block (goniosynechiae) without primary pupillary block and cases of canal block meaning obstruction of aqueous humour flow through Schlemm s canal there being no signs of obstructed circulation of aqueous humour elsewhere i e normal gonioscopy

The last group is ciliary block i e cases having obstruction of aqueous hour circulation from the ciliary body to the anterior chamber due to adhesions between the ciliary process and the hyaloid membrane (Shaffer 1973)

Results

Among the 874 eyes about which data concerning the postoperative course were available 16 developed aphakic glaucoma i [illegible] 1 8 %

Out of these 16 cases 7 (44 %) were classified as pupillary block [illegible] (3[illegible] %) as canal block and 3 (19 %) as angle block (cf Table I) No case of ciliary block was found

Thus aphakic glaucoma due to pupillary block occurred in 0 8 % aphakic glaucoma due to canal block in 0 7 % and aphakic glaucoma due to angle block in 0 3 %

Table I gives information about most of the items listed under Material and Method for the 3 groups of aphakic glaucoma

As regards the group of pupillary block it should be emphasized in particular that in 6 of the 7 eyes the cataract operation included iridotomy and in only one iridectomy and that 5 eyes exhibited postoperatively increasing vitreous herniation into the pupil (cf Fig 1) Only one eye showed a shallow chamber during the first postoperative week before the tension started rising and only two eyes showed signs of postoperative uveitis

The treatment in this group was surgery in the case of 6 eyes (a total of 7 operations 4 iridectomies 2 cyclodialyses and 1 trabeculotomy) whereas the treatment of one eye was exclusively medical

All ey[illegible] of the group with canal block unlike the other two groups showed open angles without goniosynechiae In these cases therefore canal block was an exclusion diagnosis Incidentally the most striking feature of this group was the fairly high mean preoperative tension However the difference between the mean tension in this group and in the others is not statistically significant (Wilcoxon s test) The tension in 3 of the [illegible] eyes in this group was 20 23 and 2[illegible] but loss of function had not been found preoperatively and the diagnosis of glaucoma had not been made before the cataract operation In this group moreover corneal incisions had been made in 3 cases As compared with the other groups and considering that as already mentioned corneal incisions were used to a marked extent only during one of the [illegible] years under study this seems surprising The treatment in this group was predominantly medical Surgery was used on only [illegible] eyes which in return underwent a total of [illegible] operations (5 trabeculectomies and 1 cyclodialysis)

Table I
Classification and data for 16 cases of aphakic glaucoma

	No of eyes	Preop tension (mean)	Iridotomy	Iridectomy	Postop depth of chamber (1st week)		Increasing vitreous herniation into the pupil
					normal	shallow/absent	
Pupillary block	7 (44 %)	15 mm (10–18)	6	1	6	1	5
Canal block	6 (37 %)	19 mm (13–27)	0	6	6	0	1
Angle block	3 (19 %)	14 mm (8–1[illegible])	2	1	3	0	0
Total	16		8	8	15	1	6

Fig 1
Pupillary block in an aphakic eye with vitreous hernia

Fig 2
Angle block in an aphakic eye after vitreous loss

Table 1
Classification and data for 16 cases of aphakic glaucoma

Gonio synechiae	Postop uveitis	Corneo scleral incision	Corneal incision	Vitreous loss	Chymo trypsin	Treatment		
						Medical	Surgical	Medical + surgical
■ (No data for 2 eyes)	2	7	0	0	1	1	4	2
0	1	3	3	1	2	4	1	1
3	0	2	1	3	0	3	0	0
8	3	12	4	4	3	8	5	3

The small group with angle block was characterized primarily by all 3 eyes having sustained loss of vitreous and by gonioscopy showing in all cases wide goniosynechiae upwards with vitreous strings rising toward the cataract scar (cf Fig 2) Within the angle block group there was no case of a postoperatively flat chamber or choroid detachment prior to the increase of tension All eyes of this group were treated medically

None of the 16 eyes with aphakic glaucoma had had chamber haemorrhage capsular rupture or epithelization Furthermore none of the eyes exhibited pseudoexfoliation or diabetic changes The intraocular tension was normalized in all 16 eyes

Discussion

In the available reports on aphakic glaucoma the occurrence has ranged from 2 95 % (Racz Szilvassy & Pinter 1974) to 5 4 % (Cinotti & Jacobson 1953) Meyer & Sternberg (1950) found 3 52 % In a prospective study Miller Keskey & Becker (1957) found aphakic glaucoma in 7 % and it is beyond doubt that the above mentioned retrospective analyses give minimum values Except for

Racz et al (1974) none of the authors seem to have used a microsurgical technique and therefore it seems reasonable to assume that the low incidence of 1 8 % found in the present analysis is due int al to the use of microsurgery

The most common cause of aphakic glaucoma in the present series was pupillary block (44 %) which is in agreement with François (1974)

In the present series the cause of pupillary block is quite obviously the use of iridotomy instead of iridectomy (in [illegible] out of the 7 cases) This does not accord with François (1974) who states that basal iridotomy is just as effective as iridectomy Chandler & Grant (1965) and Jaffe (1972) reported that the most common cause of aphakic pupillary block was a shallow chamber post operatively In the present series this factor was of subordinate importance (found in only 1 out of the 7 cases) presumably because of a sufficient closure of the wound in the microsurgical technique

The increase of tension in 5 out of the 7 eyes with pupillary block in the present study was associated with increasing vitreous hernia but without rupture of the hyaloid membrane In 2 of these 5 cases there was at discharge 8 days after the operation no vitreous hernia It was not recorded and only as slight until at follow up 15 days postoperatively whereupon it increased In most cases the herniation was described before the abnormal increase in tension and the glaucoma was not manifest until a vitreous/cornea contact had been established In the 2 eyes in which the glaucoma developed without a vitreous hernia the increase in tension was preceded by postoperative uveitis making the pupillary edge adhere to the hyaloid membrane affected with slight postinflammatory fibrosis Unlike Shaffer (1973) therefore we feel that if the hyaloid membrane is normal vitreous hernia will always co exist with aphakic pupillary block and that manifest pupillary block is preceded by a phase of relative aphakic pupillary block characterized by increasing vitreous herniation A presupposition of such movement of part of the vitreous at a normal or slightly elevated intraocular tension must be an intermittent pressure gradient between the posterior and anterior chamber It must be assumed therefore that a relative aphakic pupillary block with intermittent stagnation of aqueous humour in the posterior chamber due to *insufficient* iridotomy/iridectomy will slowly propel the juxta pupillary part of the vitreous through the pupil and that this leads to a vicious circle resulting in *manifest* pupillary block and eventually in angle block (cf Fig 1) Accordingly it is important to diagnose relative aphakic pupillary block as treatment of this condition by mydriatics can prevent the further progression into manifest aphakic pupillary block with elevation of the tension

In a few cases attempts have been made to treat the increasing vitreous herniation by miotics in order to support the hyaloid membrane but this has

resulted in considerable exacerbation with manifest pupillary block Indeed, it is apparent from the literature (François 1971) that miotics are contra indicated in pupillary block

Let it be emphasized that stationary not increasing vitreous herniation is of no diagnostic importance in connection with relative aphakic pupillary block and does not to the same extent contra indicate miotic treatment

The second largest group in the present material is that of canal block, which makes up 37 % of the total Strangely enough no previous authors on aphakic glaucoma have found this group which is characterized by not showing any of the generally assumed causes of aphakic glaucoma We assume that in fact there is a question primarily of cases having latent simple glaucoma [illegible] the mean preoperative intraocular tension having been above that in the other groups although this difference is not significant As stated by Miller Keskey & Becker (1957) there is even after uncomplicated cataract extraction a postoperative reduction of the facility of outflow as compared with the pre operative value Therefore if the preoperative outflow mechanism is impaired an uncomplicated cataract extraction may bring the eye into a state of manifest simple glaucoma

Moreover one patient of this group developed simple glaucoma of the contralateral unoperated eye 6 months after the onset of aphakic glaucoma in the operated eye Miller Keskey & Becker (1957) have reported a similar case even with normal preoperative tonography

For the above mentioned reasons we feel that probably the obstruction to the circulation of aqueous humour in this group of eyes is localized in Schlemm s canal Hence the term "canal block

The explanation why the canal block group makes up [illegible] largest but one group of the present material is presumably that the [illegible] tension (Linner 1976) has been gaining increasing influence during the period under study (1970–76) Owing to this more relaxed attitude to the [illegible] level diurnal measurements of intraocular pressure and tonography have been omitted in the case of eyes showing tension values at the borderline [illegible] Thereby the presence of a possible simple glaucoma has not been detected preoperatively If it had been there would have been a possibility of [illegible] the necessity of simultaneous operation for cataract and glaucoma [illegible] & Shaffer 1974) Four eyes could be sufficiently treated by [illegible] medication but as already mentioned the remaining [illegible] eyes [illegible] to be subjected to a total of 5 trabeculectomies and 1 cyclodialysis [illegible] of glaucoma had been made preoperatively in these 2 cases [illegible] presumably have used combined trabeculotomy and cataract extraction [illegible] Custodis & Ditzen 1974 Frankelson & Shaffer 1971)

It is remarkable that in 3 of the [illegible] eyes with canal block a corneal cataract incision had been used as this procedure was employed during only one of the 6 years under study This might indicate that this procedure presumably if the incision is very close to the limbus does not involve a lesser risk than a corneo scleral incision of injuring Schlemm s canal

This is not in agreement with previous reports (Corydon & Duperre 1976 François 1974)

Within the small group of angle block all 3 cases had goniosynechiae of less than 180° extent upwards due to strands to the cataract scar arising through loss of vitreous (cf Fig 2) In these 3 cases gonioscopy showed an open angle downwards but deranged trabecular structure with scattered coarse pigment granules To explain the elevation of tension in these cases therefore it must be postulated that the function of the inferior 180° of the chamber angle is reduced e g by sedimentation of inflammatory products from the reaction caused by the operation in the anterior segment As none of the 3 eyes showed postoperative uveitis exceeding what is normally seen it must be assumed that this factor applies to a major or minor degree to all eyes subjected to cataract surgery Maintaining a normal postoperative tension therefore apparently presupposes normal function of the superior angle circumference

Finally it should be mentioned that there was not a single case of angle block after absence of the chamber with choroidal detachment despite the fact that choroidal detachment was largely treated merely by conservative measures

References

Chandler P A & Grant W M (1965) *Lectures on glaucoma* p 237 Lea and Fibiger Philadelphia

Cinotti A A & Jacobson J H (1953) Complications following cataract extractions *Amer J Ophthal 36* 929–936

Corydon L & Duperre (1976) Über das Verhalten des intraokularen Druckes nach der Kataraktoperation in mikrochirurgischer Technik mit kornealem Stufenschnitt und fortlaufender Nylonnaht *Acta ophthal (Kbh) 54* 215–220

François J (1974) Aphakic glaucoma *Ann Ophthal* [illegible] 429–442

Frankelson E N & Shaffer R N (1974) The management of coexisting cataract and glaucoma *Canad J Ophthal 9* 298–301

Jaffe N [illegible] (1972) *Cataract surgery and its complications* p 166 Mosby Saint Louis

Linner E (1976) Ocular hypertension I The clinical course during ten years without therapy Aqueous humour dynamics *Acta ophthal (Kbh) 54* 707–720

Mackensen G Custodis M & Ditzen K (1974) Experiences with trabeculotomy *Canad J Ophthal* [illegible] 163–169

Meyer S J & Sternberg P (1950) Secondary glaucoma after cataract extraction. *Trans amer Acad Ophthal Otolaryng 54* 326–340
Miller J E Keskey G R & Becker B (1957) Cataract extraction and aqueous outflow *Arch Ophthal 58* 401–406
Racz P Szilvássy I & Pinter E (1974) Kammerwinkelbefunde nach komplikationslosen Starextraktionen *Klin Mbl Augenheilk 164* 218–220
Shaffer R N (1973) A suggested anatomic classification to define the pupillary block glaucomas *Invest Ophthal 12* 540–542

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METHODOLOGICAL ASPECTS OF TEAR FLOW DETERMINATION BY MEANS OF A RADIOACTIVE TRACER

BY

T SØRENSEN and F TAAGEHØJ JENSEN

Theoretical considerations on a simplified biological system representing the tear pathways lead to the assumption of an exponential pattern of elimination of tracer substances from the conjunctival sac The tracer used in the present study was technetium Tc^{99m} as sodium pertechnetate The detection system consisted of a gamma camera coupled to a digital system a minicomputer and a magnetic tape unit
After instillation of 10 μl normal saline solution containing Tc^{99m} the decay of activity was followed by means of an activity time function curve to which exponential curves were approximated by the computer As a parameter for tear flow the fractional turnover rate was calculated from 7 to 15 min after instillation An initial faster elimination was found in the first 7 min following instillation Corrections for background radiation evaporation of water and transconjunctival transport of Tc^{99m} were estimated

Key words tear flow – radioactive tracer – method description – background radiation – evaporation – conjunctival transport

Since the introduction of the filter paper test (Schirmer 1903) the disadvantages of this technique have resulted in several modifications and in the development of alternative methods The main objections to the Schirmer test are the increased lacrimation caused by the filter paper and the unknown amount of tears which escape to the lacrimal passages Consequently methods causing as little irritation as possible to the eye are preferable

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Previous studies on tear dynamics using radioactive tracers

The first report on the use of radioactive tracer in the investigation of tear dynamics seems to be that of Bozoky & Korchmaros (1963) They used an Au^{198} solution and measured the build up over the lacrimal sac and the nasolacrimal duct The report being only preliminary did not give any details

In his thesis Ursing (1967) described measurements of Na^{+} disappearance from the conjunctival sac in anaesthetized rabbits However he was not able to evaluate the method to quantitative studies because the slope and shape of the curves varied within wide limits

The use of sodium pertechnetate (Tc^{99m}) in lacrimal drainage investigation was introduced by Rossomondo Carlton Trueblood & Thomas (1972) They demonstrated that excellent scintigrams could be obtained using a gamma camera with a pinhole collimator The method was considered a suitable technique for studying the tear dynamics of the drainage apparatus because the scintigraphy was performed under almost physiological conditions They suggested that the method could be used to study tear flow in a quantitative way if an appropiate detection system was coupled to the gamma camera

Using such equipment Trueblood Rossomondo Carlton & Wilson (1975) investigated the effect of various ophthalmic vehicles on corneal contact time A percentage of 2 9 of the entire activity immediately after instillation was still present after 90 seconds when normal saline solution was used as a vehicle

The effects of drug vehicles on ocular contact time have also been studied by Hardberger Hanna & Boyd (1975) They determined the half time of the initial value of radioactivity with a recording rate meter mounted on a radiation counter a half time of 4 2 min was found using saline as a vehicle Trueblood et al s results cannot be compared with those of Hardberger et al owing to a difference in the area measured and because Trueblood et al recorded over the eye from the first seconds after instillation when the very fast elimination of tracer is due to a rapid outflow of tears after the addition of saline to the normal tear volume Trueblood et al s region of interest was the cornea – not the whole conjunctival sac Unfortunately Hardberger et al did not mention their region of interest

The region of interest technique was also used by Dressler & Denffer (1974) In a preliminary report they indicated a half time of approximately one minute for the conjunctival sac area using a normal saline solution as a vehicle

A comparative study of contrast dacryocystogram and nuclear dacryocystogram has been performed by Chaudhuri et al (1975) on 21 patients who had symptoms of obstruction in the lacrimal drainage system However no dynamic investigations on tear flow were performed by these authors A similar study has been performed by Brizel et al (1975) who measured transit times for the appearance of technetium in the lacrimal sac and duct no tear flow determinations were done Such studies have been performed by Meyer & Dausch (1975) on 105 patients (73 with normal tear pathways) Their conclusions were that statements on tear flow dynamics could not be made using technetium in normal saline Their negative results were probably due to a low specific activity (50 μCi Tc^{99m} in 10 μl normal saline) and resulting low count rates A study on quantitative lacrimal scintigraphy has been published by Hurwitz Maisey & Welham (1975) They used Tc^{99m} in colloid sulphur as tracer a gamma camera and a computor for evaluating the dynamics of the lacrimal drainage A tear flow for the conjunctival sac was not measured since they had chosen a rather small

area of interest placed on the inner canthus resulting in a half time of 4 1 min corresponding to a fractional turnover rate of 0 17 min^{-1} in seven normal patients in the erect position Unfortunately Hurwitz et al had very low count rates and probably relative high background radiation Their determination of the fractional turnover rate might therefore be too low

The purpose of this paper is to describe a method to estimate tear flow using a radioactive tracer The method being apparently non irritating may be considered physiological The method has been applied on normal subjects These results will be published in another paper Since the tear flows obtained are low the influence of background activity transconjunctival transport of Tc^{99m} and evaporation of water is estimated

A simplified tear pathway model

Several authors have assumed an exponential pattern of dye elimination from the conjunctival sac in their calculations on tear flow (Kirchner 1964 Mishima et al 1966 Brandt & Fritsche 1967) An empirical explanation of this hypothesis was given by Mishima et al (1966) Since apparently the theoretical background for the assumption of an exponential elimination has not been published before a description of tear pathway model may be appropriate

The lacrimal system may be simplified as illustrated in Fig 1 The system is assumed to be in steady state with a constant volume in the conjunctival sac of V (μl) a constant tear secretion of L (μl min^{-1}) a constant tear drainage via the canaliculi of L (μl min^{-1}) and a recorded amount of tracer of Q and Q_t at the beginning of the experiment and at time t respectively

The amount Q of tracer activity in the conjunctival sac gives a concentration of $\frac{Q}{V}$ assuming complete mixing With an outflow of L (μl min^{-1}) the amount leaving the sac per unit of time will be $\frac{Q}{V}L$ This amount can also be expressed as dQ and

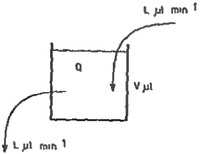

Fig 1
The simplified biological system representing a conjunctival sac with a constant tear volume a constant tear secretion and a constant tear drainage

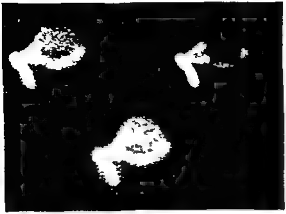

Fig 2

Scintigram of a normal left eye Radioactivity can be seen in the conjunctival sac and the lacrimal passages but the radioactivity has not entered the nose Three scintigrams with different degrees of exposure are shown

therefore

$$\frac{dQ}{dt} = -\frac{Q}{V} \cdot L \qquad \text{or (1)}$$

$$\frac{dQ}{dt} + \frac{L}{V} \cdot Q = 0 \qquad (2)$$

If $\frac{L}{V} = k$ (min^{-1}) equation (2) can be intergrated to

$$Q_t = Q_0 \cdot e^{-kt} \qquad (3)$$

k being the fractional turnover rate and e the base of natural logarithm

Applied method

The individual to be examined was placed in the supine position with the eye approximately 3 cm from the collimator The head was fixed in a plaster bandage and slightly turned to the side opposite to the eye being investigated to avoid pooling in the lateral canthus

A volume of 10 μl of a physiological saline solution containing 200 μCi Tc^{99} elute was placed on the center of the cornea with a Hamilton syringe The solution was non irritating and no anaesthesia was used During the instillation the eyelids were retracted manually to avoid trapping of technetium in the eyelashes

The distribution of the radioisotope could be seen continuously on a persistent oscilloscope display (Fig 2) The data system made it possible to follow the changes in radioactivity The "region of interest" could be assigned arbitrarily by the operator using marker lines on the computer oscilloscope The as

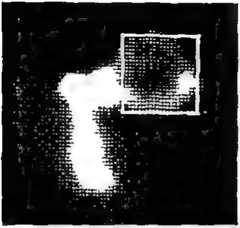

Fig 3
The region of interest corresponding to the conjunctival sac is placed within the white frame

signed area over the conjunctival sac can be seen in Fig 3 The radioactivity within this area was accumulated for ten second intervals and serially stored on a magnetic tape The accumulated amount of activity in each ten second interval was expressed as counts/10 seconds The resultant 90 numbers were *plotted as an activity time function curve (Fig 4) for the designated conjunctival* sac area

Fig 4
The activity time function curve and the curve approximated to the actual curve in the time interval 7 to 15 min

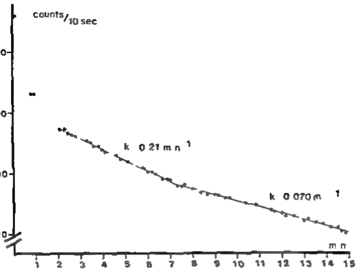

Fig 5
The activity time function curve in a semilog plot

Semilog plots of activity versus time (Fig 5) showed that in all cases a straight line could be approximated to the curve at the time interval 7 to 15 min However in the vast majority of cases the whole decay could not be expressed by a single straight line but by two straight lines The one mentioned from 7 to 15 min after instillation and another from about 2 to 5 min after instillation with a greater slope

The data system was programmed to approximate an exponential curve by the method of least squares to the actual activity decay curve (Fig 5) The slope of the straight line from 7 to 15 min – k value in equation (3) – and the standard deviation of this value was calculated by the computer The slope in the initial phase was approximated manually since the position of the straight line interval was not always fixed to the 2 to 7 min interval as shown in Fig 5

In the very first seconds or minutes the elimination was very fast due to the rapid outflow of tears from the high tear volme after the instillation

Using the values shown in Fig 5 the amount of tear flow in the basal phase could be calculated to be about 0 5 μl min $^{-1}$ the tear volume in the conjunctival sac assumed to be 7 μl (Mishima et al 1966) In the initial phase the tear flow was found to be 1 4 μl min $^{-1}$

This calculation is rough and needs corrections as shown later in the text.

Detection system

The detection system consisted of a gamma camera (Pho/Gamma III High performance Nuclear Chicago Corp) with a pinhole collimator coupled to a digital system (50/50 Nuclear Data Corp) Recording and storage of information were controlled by a minicomputer (PDP 8/L Digital Equipment Corp) The data were delivered for long term storage on a magnetic tape (Ampex tape unit TM7)

Evaluation of method

Radioactive tracer and dosimetry To determine the fractional turnover rate k in the conjunctival sac radioactive technetium Tc^{99m} was utilized This isotope is commonly available in nuclear medicine departments as it is widely used in brain scintigraphies Tc^{99m} has a half life of [redacted] h and is primarily a gamma emitter The radioactivity was eluted from a Mo^{99}/Tc^{99m} generator as sodium pertechnetate An instillation in the conjunctival sac of 200 μCi of the Tc^{99m} eluent was calculated to produce a dose to the lens of 380 mrad if the isotope had an effective half time of 15 min and was located 3 mm in front of the lens Spreading of the technetium in the conjunctival sac and an actual half time of a few min will make the actual lens dose much smaller Furthermore the eyes were washed after the determination This very small dose can be regarded as harmless and repeated investigations can safely be performed

Influence of instilled volume The influence of the instilled volume on the shape and slope of the activity time function curve was studied by instillation of 5 μl and 15 μl technetium solution on the same subject The shape of the curves was found not to be influenced by the volume instilled

Table I
Fractional turnover rate in 5 subjects after instillation of 5 and 15 μl

5 μl	15 μl
k min^{-1}	k min^{-1}
0 079	0 122
0 066	0 062
0 069	0 089
0 072	0 076
0 061	0 078

The values for the fractional turnover rate in the physiological phase can be seen in Table I Though the λ value seems to be higher when using 15 μl no conclusions can be drawn from this small group of determinations (t test for pair differences $P \sim 0\ 1–0\ 2$)

Corrections for background components The background components consist of (Ursing 1967)

1 Natural background activity ($B_{nat\ 1} = B_n$)

2 Background activity remaining in the individual from previous determina tions ($B_{rem} \quad g = B$)

3 Background activity representing the amount of tracer fixed to the site of the deposit ($B_{mat} \quad = B_m$)

4 Background activity dependent on the redistribution of the radioisotope (B_t at time t and B_f the final value of B_t at the end of the elimination from the eye)

The natural background B_n was found to be so low that no correction for this activity was considered necessary (6 counts/10 seconds)

In tear flow determinations done successively – the second starting two min after the end of the first determination – it was assumed that the technetium remaining in the conjunctival sac from the first measurement was completely mixed and eliminated with the second technetium deposit Consequently cor rections for B_r were not performed

The background activity B_m represents the amount of tracer adherent to the conjunctival cells the mucous thread and the activity that might have entered the eye Attempts to determine B_m were done by washing the con junctiva with a saline solution after the tear flow determination followed by a measurement of $B \ + B_m$ This value was found to decrease more than the physical half life of technetium could explain In five subjects the fractional turn over rate was found to be 0 016 min^{-1} (range 0 010 to 0 027) When corrected for background radiation this value was found to be 0 020 min^{-1} – a value of the same magnitude as the transport of Tc^{99m} to the blood (see later in the text)

This decrease in activity could be explained by an inadequate conjunctival washing and by a transport of technetium from the conjunctival cells and the anterior chamber to the blood Since it may be assumed that B_m forms a smaller percentage of the deposit during the 15 min measuring time no corrections have been performed

The increase of B_t due to redistribution of the technetium that have entered the general circulation may be supposed to follow the equation

$$B_t = B_f \quad (1 - e^{-kt}) \qquad (4)$$

The equation is only an approximation owing to a distribution of technetium outside the circulation

The recorded number of counts at time t (Q_t) is determined by

$$Q_t - B_n = A_o \quad e^{-kt} + B_f \, (1 - e^{-kt}) \tag{5}$$

where A_o is counts/10 seconds representing the deposit at time o

Using the region of interest shown in Fig 3 the physical background radiation has been found to be 6 counts/10 seconds In four patients B_t has been determined after an injection of 200 μCi into a cubital vein The background activity rose to 24 counts/10 seconds in less than one min and thereafter remained at this level for at least 15 min These 24 counts/10 seconds can be regarded as representative for $B_f + B_n$ and consequently $B_f = 18$ counts/10 seconds Using equation (5) the fractional turnover rate would be corrected from 0 070 min^{-1} to 0 072 min^{-1} This correction is in fact too high because in equation (5) it was assumed that the k value for tear flow determination and the k value for the transport of technetium to the blood were equal This assumption is not true The fractional turnover rate representing the transport of technetium to the blood has been found to be approximately 5 times smaller than the fractional turnover rate in tear flow determination (unpublished data) It therefore seems reasonable not to make any corrections for background radiation due to redistribution of the isotope

Correction for Tc^{99m} half-life The half life of Tc^{99m} is about 6 h corresponding to a fractional turnover rate k_{Tc} of 0 0019 min^{-1} The k values measured should be corrected for this k_{Tc}

Correction for disappearance to the blood via the transconjunctival route In 11 patients with their lacrimal sacs removed a mean fractional turnover rate of 0 021 min^{-1} has been found Since the recorded activity from these patients was very high no background correction was necessary The fractional turnover rate in patients without lacrimal sacs represents the fraction of the technetium in the conjunctival sac that has been transported from the region of interest to the blood i e the transconjunctival transport of technetium A correction of the tear flow determination for this transport would be rather hypothetical since nothing specific seems to be known about water transport across the conjunctiva

Evaporation Tear flow calculated from the fractional turnover rate needs a correction for evaporation of water from the tear film as technetium itself cannot evaporate This influence of water evaporation cannot be estimated with the present tracer technique The values reported in the literature are few and vary within wide limits Schirmer (1903) found an evaporation of

0 27 g in 16 h (0 28 μl/ min) at a temperature of 18°C from a saline solution in a beaker (2 35 cm in surface area)

In experiments on rabbits von Bahr (1941) found an evaporation of 1 μl min $^{-1}$ while Mishima & Maurice (1961) measured an evaporation 10 times less – 0 1 μl min $^{-1}$ (3 μl hour^{-1} cm^{-}) Mishima & Maurice also found that the evaporation would increase 15 times if the lipid layer of the precorneal film was removed Schirmer did not pay attention to the lipid layer and von Bahr measured the evaporation in a stream of dry air Thus the value of about 3 μl hour^{-1} cm seems most reasonable On the other hand Brown & Dervichian (1969) could not find any significant reduction of evaporation when secretion expressed from human tarsal glands was spread over a saline solution in beakers They found an evaporation about 50 μl hour^{-1} cm^{-} at temperatures between 35° and 42°C – a value of the same size as that of Mishima and Maurice in rabbits with removed lipid layer Brown & Dervichian stored their secretion in a refrigerator before application Their *in vitro* experiments with a not clearly defined lipid layer cannot be completely compared to the *in vivo* conditions

Mishima & Maurice measured corneal thickness changes and deduced the evaporation rate whereas Iwata et al (1969) determined the evaporation in rabbits by weighing the evaporated water which had been absorbed by anhydrous CaCl The evaporation was found to be of the same amount as reported by Mishima and Maurice though only a fourfold increase of evaporation could be found when the lipid layer was removed

Discussion

The correct determination of tear flow by the described method can only be achieved if the system is in steady state This is probably a reasonable assumption in normal persons with a capacity of tear drainage many times that of tear secretion under basal circumstances Mishima et al (1966) found that the tear volume only increases slightly with increasing tear flow The calculated tear flow would be too low if the tear volume was in fact increasing at the time of measurement

It was assumed that a complete mixing of technetium with the tears took place This error is also present in methods using dye dilution measurements Mishima et al developed a technique allowing for the determination of tear flow by means of a specially designed fluorophotometer Their region of interest was a small area in the lower marginal tear strip Mishima et al s elimination curves had the same diphasic shape as shown in this paper They instilled 1 μl of 1 % fluorescein in the conjunctival sac and measured the dye concentration in the lower marginal tear strip The time decay in fluorescein

concentration was interpreted in terms of an exponential elimination In the majority of cases the authors found that an initial rapid decay was followed by a slower decay after 4 to 5 min The fractional turnover rate of tears in the slower physiological phase was calculated to be about 16 % min^{-1} with an estimated conjunctival tear volume of 7 μl corresponding to a tear flow of 1 2 μl min^{-1}

If technetium was trapped in the eyelashes the k value would decrease several times This error could be eliminated by fixing the eyelids manually during instillation and by asking the subject not to blink forcibly during the first seconds Activity trapped outside the conjunctival sac was easily visualized on the oscilloscope as a localized high activity A considerable number of experiments were discarded on this account when the volume instilled was 15 μl The instillation of only 10 μl almost overcame this problem

Alterations in counting geometry were considered of minor importance Only one determination was discarded for this reason The error of an accidental displacement of the subject can be avoided by comparing the first and the last ten second picture on the oscilloscope

The problems concerning different transport rates of water and pertechnetate across the conjunctiva have not been dealt with

The method described is based on more than 150 determinations on normal individuals (Sorensen & Taageho) Jensen 1975 1976) It is highly objective the only subjective procedure is the approximation of the straight line to the semilog plot in the initial phase

The supine position of the individual was chosen since this position was considered the most stable A subject displacement was more easily obtained in the upright position A possible gravitational influence on tear drainage will be described in a future publication A displacement of the eye away from the gamma camera was not possible since the head was fixed in a plaster bandage

This apparently non irritating method yields information on tear flow in the normal eye The initial high fractional turnover rate is interpreted as a normal reaction of increased tear flow due to stimulation of the eye at the moment of instillation since non significant differences were found instillating various volumes and since patients with Sjogren s syndrome do not seem to have this initial phase This interpretation seems to be in accordance with the results of other authors who instillated volumes of 1 μl 20 μl and one drop (27 gauge needle) in the conjunctival sac (Mishima et al 1966 Dressler & Denffer 1974 Hardberger et al 1975 respectively)

Considering the small radiation dose to the lens the present method is almost harmless The tear flow determination including computer calculations can be completed in less than half an hour

Taking into account the natural half life of the isotope and the evaporation the estimated tear flow in the basal phase (values from Fig 5) will be 0 6 μl/min

The values presented in this paper suggest that the tears in the conjunctival sac are in a state of delicate balance To approach this problem further studies on tear flow determinations in normal persons are being carried out

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References

Bahr G von (1941) Konnte der Flussigkeitsabgang durch die Cornea von physiologischer Bedeutung sein? *Acta ophthal (Kbh) 19* 125–134

Bozoky L & Korchmaros I (1963) Über die Untersuchung der Tranenableitung mittels radioaktiver Isotope *Zbl ges Ophthal 87* 185

Brandt H P & Fritsche B (1967) Klinische Erfahrungen mit dem Tranenstreifen verdunnungstest von M S Norn. *Acta ophthal (Kbh) 45* 167–176

Brizel H E Sheils W C & Brown M (1975) The Effects of Radiotherapy on the Nasolacrimal System as Evaluated by Dacryoscintigraphy *Radiology 116* 373–381

Chaudhuri T K Saparoff G R & Dolan K D (1975) A comparative study of contrast dacryocystogram and nuclear dacryocystogram *J Nucl Med 14* 605–608

Dressler J & Denffer H V (1974) Erste Erfahrungen mit der Funktionsszintigraphie der Tranenwege *Radioaktive Isotope in Klinik und Forschung 11* 378–381

Hardberger R Hanna C & Boyd C M (1975) Effects of drug vehicles in ocular contact time *Arch Ophthal (Chicago) 93* 42–45

Hurwitz J J Maisey M N & Welham R A N (1975) Quantitative lacrimal scintillo graphy *Brit J Ophthal 59* 308–312

Iwata S Lemp M A Holly F J & Dohlmann C H (1969) Evaporation rate of water from the precorneal tear film and cornea in the rabbit *Invest Ophthal 8* 613–619

Kirchner C (1964) Untersuchungen uber das Ausmass der Tranensekretion beim Mens chen *Klin Mbl Augenheilk 144* 412–417

Maurice D M (1973) Electrical potential and ion transport across the conjunctiva. *Exp Eye Res 15* 527–532

Maurice D M (1973) The dynamics and drainage of tears *Int Ophthal Clin 13* 103–116

Meyer P B & Dausch D (1975) Klinische Erfahrungen mit der Radionucleid Dacryo cystographie *Klin Mbl Augenheilk 167* 421–426

Mishima S & Maurice D M (1961) The oily layer of the tear film and evaporation from the corneal surface *Exp Eye Res 1* 39–45

Mishima S Gasset A Klyce S D & Baum J L (1966) Determination of tear volume and tear flow *Invest Ophthal 5* 264–276

Rossomondo R M Carlton W H Trueblood J H & Thomas R P (1972) A new method of evaluating lacrimal drainage *Arch Ophthal (Chicago) 88* 523–525

Schirmer O (1903) Studien zur Physiologie und Pathologie der Tranenabsonderung und Tranenabfuhr *von Graefes Arch Ophthal* 56 197–291
Sørensen T & Taagehøj Jensen F (1975) Determination of tear flow using a radioactive tracer *Acta ophthal (Kbh) Suppl* 125 43–44
Sørensen T & Taagehøj Jensen F (1976) Determination of tear flow using a radioactive tracer *Exp Eye Res* 22 297
Trueblood J H Rossomondo R M Carlton W H & Wilson L A (1975) Corneal contact times of ophthalmic vehicles *Arch Ophthal (Chicago)* 93 127–130
Ursing J (1967) On the disappearance of radiosodium ions from conjunctival and subconjunctival deposits in the rabbit A methodological study *Berlingska Boktryckeriet Lund* p 70

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NORMAL VALUES IN CLINICAL ELECTROOCULOGRAPHY

IV Analysis of Two Dimensionless EOG Parameters and Their Relation to Other Variables

BY

ERIK KROGH

Two EOG parameters – The Arden ratio (A) and an expression devised by Gliem (G) – from a sample of normal human subjects are studied Their relations to the EOG potential and time parameters and to sex age pupillary diameter degree of iris pigmentation refractive error and axial length ocular protrusion and interpupillary distance were assessed. Right eye and left eye distributions were congruent although individual differences were sometimes appreciable, especially in the case of G The two ratios were positively correlated and both showed a negative correlation to the interval between the dark trough and the light peak Correlations to the EOG potential parameters especially the light induced potential rise of the dark adapted eye were also established

In the case of A a higher level was disclosed in the male half of the sample A negative age correlation predominant in the female part of the sample characterized both ratios The two ratios were positively correlated to the pupil diameter negatively correlated to the degree of refractive error and positively correlated to the degree of ocular protrusion The consequences for the clinical EOG test are discussed and it is concluded that the present EOG procedure is a qualitative rather than a quantitative test

Key words electrophysiology – electrooculography – EOG – dimensionless EOG parameters – EOG ratios – Arden ratio – Gliem ratio – normal range – statistical analysis

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In the evaluation of the electrooculogram (EOG) two or more potential figures are often combined into a dimensionless quantity in order to obtain a parameter with less dispersion than the voltage values A previous paper (Krogh 1977) presents the frequency distributions of two such quantities – the Arden ratio (A) (Arden et al 1962) and the Gliem ratio (G) (Gliem 1971) – derived from a sample of normal human subjects and discusses their advantage as compared with the potential parameters The two ratios are formed by the following elements the base potential value (B) measured according to Gliem (1971) the minimum value (D) during dark adaptation and the maximum value (L) during light adaptation They are expressed as $\frac{L}{D} \times 100$ (A) and $\frac{L\,D}{B} \times 100$ (G) The foreseen reduced dispersion could be demonstrated only in the case of A and even for this parameters an appreciable scale width had to be accepted There is therefore reason to further investigate the normal behaviour of these ratios

This paper is concerned with statistical analysis of the two ratios A and G including their relations to other sample variables First the general and individual differences between right eye and left eye values are assessed followed by an investigation of the relations between the ratios and the EOG potential and time parameters of the same sample Next the possible connexions between the ratios and the following variables sex age pupillary diameter degree of iris pigmentation refractive error and axial length ocular protrusion and interpupillary distance are evaluated Finally the clinical EOG interpretation is discussed in the light of the present findings

Material

The test sample comprises 142 eyes (72 subjects an equal number of females and males and an age span of 13–81 years) without any signs of pathological eye changes or diseases with ophthalmological implications A detailed description of the sample and the selection procedure is given in an earlier paper (Krogh 1975a) and the potential and time parameters have been analysed separately (Krogh 1976) The sample median and range of the two ratios are A 241 (148–449) and G 88 (34–167) (Krogh 1977)

Methods

RECORDING TECHNIQUE

The EOG potentials were picked up by lead alloy electrodes and amplification and display were performed by a Mingograph III 34 (Siemens) provided with EMT 1° B preamplifiers A DC input was employed (bandwidth 0–15 Hz) which excluded any

Table I

Some characteristic figures of individual side differences of the *Arden and Gliem ratios All differences are counted as positive* The sample medians of *A* and *G* are 241 and 88 respectively

	Median value	90 percentile	Maximum value
Arden ratio $\frac{L}{D} \times 100$ (N = 149)	22	83	172
Gliem ratio $\frac{L-D}{B} \times 100$ (N = 111)	14	35	[illegible]6

influence of variations in eye movement velocity upon the amplitude of the recorder deflections and which further allowed irregularly performed saccades to be measured with accuracy However (because of limited possibilities for DC compensation) this meant that only 111 *B* values could be recorded (Krogh 1975a b) The stimulus light yielded 4000 lx in the central part of the gaze field decreasing to 2500 lx in the peripheral part measured at the eye level of the subject It was switched on in a 10 min pre adaptation period whereafter the base value was recorded The following dark period was terminated when the dark trough value could be demonstrated Light was then switched on again until the light peak potential was passed Two time parameters were also recorded 1) the interval between the beginning of the dark adaptation and the occurrence of *D* and 2) the interval between *D* and *L*.

STATISTICAL EVALUATION

The distribution free statistical tests were performed by means of electronic data processing (Statistical Section Rigshospitalet) The hypothesis of no scale shift between two or more sets of data was tested by the following methods Mann Whitney s test for two independent sets of observations Wilcoxon s test in case of paired observations and Kruskal Wallis test for three or more independent sets of observations The hypothesis of no monotonic relationship in two sets of observations was evaluated by Spearman s rank correlation test expressed as a coefficient (r) Finally the hypothesis of equal dispersion around the medians of two sets of observations was estimated by Westenberg s interquartile range test (Siegel 1956 Bradley 1968)

Table II

Correlations between the Arden and Gliem ratios mutually and between these quantities and the EOG potential and time parameters

	Base value	Dark trough	Light peak	Difference between light peak and dark trough	Interval between beginning of dark adaptation and dark trough	Interval between dark trough and light peak	$\frac{L}{D} \times 100$
Gliem ratio $\frac{L\ D}{B} \times 100$ (N = 111)	$r_s = -0.15$ $P > 0.1$	$r_s = -0.24$ $P = 0.01$	$r_s = 0.25$ $P = 0.008$	$r_s = 0.50$ $P < 0.001$	$r_s = -0.14$ $P > 0.1$	$r_s = -0.31$ $P < 0.001$	$r_s = 0.78$ $P < 0.001$
Arden ratio $\frac{L}{D} \times 100$ (N = 149)	$r_s = 0.11$ $P > 0.2$	$r = -0.40$ $P < 0.001$	$r_s = 0.27$ $P = 0.001$	$r_s = 0.63$ $P < 0.001$	$r = -0.003$ $P > 0.9$	$r_s = -0.23$ $P = 0.007$	

For the discussion a 0 05 limit of significance was selected but the P values are always stated A two tailed significance estimate was used with the exception of Kruskal Wallis test which is assessed by an upper tail region of rejection only

Positively correlated data from right and left eyes cannot be treated as independent observations when related to subject linked variables such as sex age and inter pupillary distance In such cases the average of the individual right and left eye values was used in the statistical analysis This procedure halves the number of observations but in return the resulting data are subject to less variation (in two subjects where only one eye fulfilled the criteria for inclusion in the sample the single values were used)

Results

RIGHT AND LEFT EYE CONCORDANCE

The differences between the right and left eye sample medians were not significant for any of the two relative expressions (Wilcoxon s test $P > 0\ 4$ in both cases) Further the degree of scatter around the right and left eye medians did not differ significantly (Westenberg s test $P > 0\ 3$ in both cases) Individual right left differences are exemplified in Table I

RELATIONS TO OTHER EOG PARAMETERS AND TO SOME SUBJECT OR EYE LINKED VARIABLES

The correlation between A and G and between these parameters and the EOG potential and time figures are given in Table II expressed as rank correlation coefficients With the exception of B the potential factors are all correlated with the dimensionless quantities according to their mathematical connexion Both ratios show a high correlation to the light induced potential rise (L D)

Sex

The level of the Arden ratio was significantly higher in the male part of the sample (Table III)

Age

Table IV gives the medians of the two dimensionless expressions in each of the seven age groups The figures indicate a decline with increasing senescence and the negative correlations were significant ($r_s A = -0\ 43$ $P < 0\ 001$ $r_s G = -0\ 46$ $P < 0\ 001$) The correlations were re tested in the female and male halves of the sample and were now apparent among the women only ($r_s A = -0\ 57$ $P < 0\ 001$ $r_s G = -0\ 61$ $P < 0\ 001$) For the men $r_s A = -0\ 14$ $P = 0\ 2$ and $r_s G = -0\ 32$ $P = 0\ 09$

Table III

Median values of the Arden and Gliem ratios for each sex separately. The figures and the significance calculations are based on the average of the individual right and left eye values

	Arden ratio $\frac{L}{D} \times 100$ (N = 149)	Gliem ratio $\frac{L\ D}{B} \times 100$ (N = 111)
Females	235	85
Males	260	9[illegible]
Mann Whitney's test	$P = 0.04$	$P > 0.1$

Table IV

Median values of the Arden and Gliem ratios for each of the seven age groups. Both ratios showed a negative correlation to age ($r_s A = -0.43$, $r_s G = -0.46$, $P < 0.001$ in both cases). The figures and the significance calculations are based on the average of the individual right and left eye values

	10–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	≥ 70 years
Arden ratio $\frac{L}{D} \times 100$ (N = 149)	275	245	279	255	236	204	190
Gliem ratio $\frac{L\ D}{B} \times 100$ (N = 111)	9[illegible]	91	97	88	86	72	67

Pupillary diameter

Positive correlations were found between the pupillary diameter and A and G respectively (r $A = 0\,33$ $P < 0\,001$ r $G = 0\,36$ $P < 0\,001$)

Iris pigmentation

The sample was divided into four groups according to the degree of iris pig mentation (Tocher 1908) Employing Kruskal Wallis test no significant dif ferences between the levels of the four sub groups were found ($P = 0\,07$ and $0\,1$ for A and G respectively)

Refractive error and axial length

A negative correlation between the degree of refractive error and the two dimensionless expressions was found ($r_s A = -0\,19$ $P = 0\,02$ r $G = -0\,21$ $P = 0\,03$) No correlation was found between the axial length of the eye as measured with ultrasonography and the two relative EOG quantities (r $A = 0\,15$ $P = 0\,1$ r $G = 0\,13$ $P = 0\,2$)

Ocular protrusion

A positive correlation existed between the ocular protrusion measured a m Hertel and the two ratios (r $A = 0\,27$ $P = 0\,001$ r $G = 0\,27$ P $0\,004$)

Interpupillary distance

No correlations between this variable and the two ratios were demonstrable in this study ($P > 0\,4$ in both cases)

Discussion

The present investigation has demonstrated a good congruence between the right and left eye distributions of the two dimensionless EOG expressions This corresponds with the similar result of an analysis of the potential para meters (Krogh 1976) The individual side differences are however appreciable and must be taken into consideration in the interpretation of a bilateral test Moreover as no or only minor differences exist between each subjects right and left eye with respect to the variables not pertaining to the EOG the figures in Table I suggest a low intra individual precision of the present EOG recording procedure This has also been claimed in earlier investigations

(Kelsey 1967 Muller & Haase 1970) still they contain other explanations as well of the intra individual scattering (AC amplification with small time constant submaximal light stimulus) Finally the two ratios disclose different degrees of right left difference If the figures in Table I are compared with the respective sample medians of A and G the percentile values of the latter are proportionally the largest

The correlations between the relative and absolute EOG parameters (Table II) are notable in several respects For example Arden & Barrada (1962) found no correlation between D and the Arden ratio (the relation to L was not examined) and argued that the actual potential recorded does not influence the ratio This conclusion is not necessarily contradicted by accepting the relation now indicated because obviously some kind of a mean potential must be used in the argument Accordingly no correlation is found between the parameter $\frac{L+D}{2}$ and the Arden ratio in the present study ($P = 0\,4$)

The lack of correlation between the Gliem ratio and B in the present study might be due to a limited scale width of B as compared with the other potential parameters However this explanation is not valid (Krogh 1975a) Furthermore the scatter diagram of B versus G depicts a parabolic relation with the largest base values occurring in the central region of the G scale No explanation of this phenomenon is possible within the framework of the present investigation.

The negative correlation between the Arden ratio and the interval between the dark trough and the light peak finds support in the statement of Arden & Barrada (1962) that abnormally long peak times (over 11 min) are always associated with low ratios This was claimed by Taumer et al (1974a b) to be a consequence of exciting a resonating system characterized by individually varying resonance frequencies by fixed dark and light periods However the present EOG method using individually timed dark periods should afford good conditions for resonance The statistical evidence in the present and earlier investigations (Krogh 1976) of a relation between the age of the subject and the Arden ratio as well as the interval between D and L corresponds with their mutual connexion but in principle questions of causality cannot be answered by statistical surveys

Kolder & Hochgesand (1973) found no significant Arden ratio differences between female and male subjects ($N = 37$) Adams (1973) found a significantly higher A level in the female half of his sample ($N = 120$) A comparison between the mean values of A in the ten year age groups common to Adams's study and the present one reveals a close correspondence with regard to the females whereas the male values in this material exceed those of Adams's sample by 40–60 units in all groups It can be recalled that the male part

of the present sample showed a significantly lower D level (Krogh 1976) Gliem (1971) did not determine the level of G in each sex separately

Arden & Barrada (1962) found a negative correlation between age and the Arden ratio ($r=-0\ 297$ $P<0\ 05$) In the normal sample of Reeser et al (1970) the apparently smaller ratios in the older subjects showed no significant difference from those of the younger Adams (1973) did not find any age correlation in the total sample of Arden ratios but those of the females showed a decline with age ($r=-0\ 27$ $P<0\ 01$)

The negative correlation in the present sample between A and age agrees with the earlier demonstrated positive correlation between age and D level still the predominantly female contribution to this characteristic does not find support in the analysis of the influence of sex on the EOG potentials (Krogh 1976)

A positive correlation between the pupillary diameter and the Arden ratio can be anticipated as a consequence of a submaximal light stimulus The presently employed EOG procedure is however designed and tested against this source of variation (Krogh 1975a) Besides the two variables are related to the age of the test subject according to their mutual connexion (in case of age versus pupillary diameter $r=-0\ 81$ $P<0\ 001$)

Geijer Mannerfelt & Pallin (1967) did not find any significant correlation between the Arden ratio and the axial length of the eye Alexandridis et al (1975) compared one sample of subjects with myopic anisometropia with another one with hypermetropic anisometropia Their results are difficult to interpret as the mean Arden ratio levels of both the more hypermetropic (2 1) and of the more myopic (2 2) eyes were (significantly?) smaller than those of the two groups of contralateral control eyes (2 28 and 2 38 respectively) The authors emphasize that the myopic eyes did not show retinal degenerations In the same paper a sample of subjects with unilateral ocular protrusion was examined but no significant A differences between the protruding and the contralateral control eyes were found

The presently demonstrated negative correlation between the degree of refractive error and the Arden ratio level is an isolated finding inasmuch as it cannot be deduced from the analysis of the potential parameters (Krogh 1976) or from a significant correlation between the axial length of the eye and A The same remarks are valid for the positive correlation between the ocular protrusion and the A level However the less hypermetropic/more myopic eyes generally protrude more ($r=-0\ 28$ $P<0\ 001$) The similar findings in case of G are in agreement with the analysis of the light induced potential rise ($L\ D$) (Krogh 1976) No clues to explain these relations are to be found in the present or other studies

Concluding

In the present study possible seasonal and diurnal causes of variation have largely been eliminated and the influence of varying eye movement velocity has been avoided by the use of DC amplification (Krogh 1975a b) Even so the dispersion of the two dimensionless EOG quantities under study is considerable and is only to a minor degree explained by the relations now disclosed In the author s opinion this makes any subdivision of the normal range according to the sex age and other attributes of the test subject of no value

Although Reeser et al (1970) have described supernormal Arden ratios in cases of albinism and aniridia it is the lower limit of that which can be accepted as normal that has particular interest A convenient limit of the Arden ratio of a single EOG recording based on the present study would be 150 representing the 2 1 percentile In case of the Gliem ratio 38 represents the 1 8 percentile

Furthermore a large right left difference does not necessarily mean a dysfunction of one of the eyes With reference to the present study values of 90 in case of the Arden ratio and 40 in case of the Gliem ratio (approximately the 95 percentiles) must be accepted as normal In Adam s study (1973) 95% of the subjects showed an Arden ratio side difference of 80 or less the difference between the two 95 percentile values corresponds with the different Arden ratio levels in the two studies (Adams 1973 Krogh 1977)

On the whole it seems as though the EOG recording in the present form must be considered a qualitative rather than a quantitative test and that the normal inter and intraindividual variation leaves a comparatively small part of the scale range available for reasonably safe indications of pathological conditions in the posterior half of the eye Probably an important means to reduce the boundary zone between normal and pathological would be to make repeated recordings in each case and use a central value of the parameter in the evaluation The practical difficulties connected with such a procedure suggest that interest might more fruitfully be directed towards the investigation of other EOG recording and/or evaluation procedures

List of abbreviations

B = base value recorded after 10 min of pre adaptation
D = dark trough the lowest potential during dark adaptation
L = light peak the largest potential during illumination
L D = the light induced potential rise

A = the Arden ratio = $\frac{L}{D} \times 100$ $\qquad$ G = the Gliem ratio = $\frac{L\ D}{B} \times 100$

References

Adams A (1973) The normal electro oculogram (E O G) *Acta ophthal (Kbh) 51* 551–561

Alexandridis E Ariely E & Gronau G (1975) Einfluss der Bulbuslage und der Bulbuslange auf das EOG *Albrecht v Graefes Arch klin exp Ophthal 194* 237–241

Arden G B & Barrada A (1962) Analysis of the electro oculograms of a series of normal subjects *Brit J Ophthal 46* 468–482

Arden G B Barrada A & Kelsey J H (1962) New clinical test of retinal function based upon the standing potential of the eye *Brit J Ophthal 46* 449–467

Bradley J V (1968) *Distribution free statistical tests* Prentice Hall New Jersey

Geijer Mannerfelt T & Pallin O (1968) On the correlation between ERG and EOG in normal eyes In Schmoger E Ed *Electrophysiology and pathology of the Visual System Proceedings of the 6th ISCERG Symposium* pp 47–51 VEB Georg Thieme Leipzig

Gliem H (1971) *Das Elektrookulogramm Ein Erfahrungsbericht* Abhandlungen aus dem Gebiete der Augenheilkunde Band 40 VEB Georg Thieme Leipzig

Kelsey J H (1967) Variations in the normal electro oculogram *Brit J Ophthal 51* 44–49

Kolder H E & Hochgesand P (1973) Empirical model of electro oculogram *Docum ophthal 34* 229–241

Krogh E (1975a) Normal values in clinical electrooculography I Material method methodological investigations and distribution of the potential and time parameters *Acta ophthal (Kbh) 53* 563–575

Krogh E (1975b) DC recording of the human corneofundal potential *Albrecht v Graefes Arch klin exp Ophthal 193* 205–215

Krogh E (1976) Normal values in clinical electrooculography II Analysis of potential and time parameters and their relation to other variables *Acta ophthal (Kbh) 54* 389–400

Krogh E (1977) Normal values in clinical electrooculography III Numerical evaluation of two dimensionless EOG parameters *Acta ophthal (Kbh) 55* 227–236

Muller W & Haase E (1970) Inter und intraindividuelle Streuung im EOG *Albrecht v Graefes Arch klin exp Ophthal 181* 71–78

Reeser F Weinstein G W Feiock K B & Oser R S (1970) Electro oculography as a test of retinal function The normal and supernormal EOG *Amer J Ophthal 70* 505–514

Siegel S (1956) *Nonparametric statistics for the behavioral sciences* McGraw Hill Kogakusha Tokyo London Sydney

Taumer R Hennig J & Pernice D (1974) The ocular dipole – a damped oscillator stimulated by the speed of change in illumination. *Vision Res 14* 63 -645

Taumer R Mackensen G Hartmann H Moser U Stehle R Werner W & Wolf D (1974) Verhalten des Bestandpotentials des menschlichen Auges nach Belichtungs anderungen *Albrecht v Graefes Arch klin exp Ophthal 189* 81–97

Tocher J F (1908–9) Pigmentation survey of school children in Scotland *Biometrika 6* 130–235

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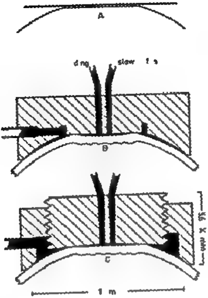

Fig 1

A) A section through the ideal model consisting of an ultraflexible spherical membrane applanated by a surface

B) A section through the type of applanating suction cup used in the rabbit experiments The applanating surface was five millimeters in diameter and plane This type but with the suction channel opening directly on the curved inner surface (and without a groove) has also been used in patients (Fig 5)

C) A section through the model used most often on human eyes It has a conical applanating surface with a top angle of 174 degrees The height of the central part can be adjusted by turning it in its eight millimeter screw thread (pitch 0 5 mm) The settings of the cup are named after its total height 5 6 + X mm

to compensate for the fact that a plane surface actually does not merely flatten the cornea when fluid is entering the interphase but makes it slightly concave The clearance could be observed by examining the applanated area with a slit lamp in blue light after colouring the fluid with fluorescein The fluid disc appeared at areas of applanation greater than approximately four millimeter in diameter (The curvature of the applanating surface is of significance for the optimum function of the cup and is at present under study) Through two small holes near the center of the surface the continuous pressure measurement and the constant inflow of isotonic salt solution (Ringer fluid) took place (Fig 2) The pressure was measured with a Statham P 23Db transducer connected to a servowriter (Servogor® Goerz Electro or Kompensograph® Siemens) The center of the eye bulb was regarded as the zero pressure level The fluid flow was delivered by a Braun Perfusor® fitted with a 10 ml syringe 1 our ml per h

was a convenient rate and was normally used The suction force was provided by letting a silastic tube (inner diameter 0 5 mm outer diameter 0 9 mm) connected to the outlet channel of the cup hang down by 20 cm. This corresponded to a siphon effect of −15 mmHg The pressure gradient due to the flow in the tube of four ml per h delivered by the pump was relatively small 1–2 mmHg A tube of similar dimensions with a length of about 15 cm connected the applanating surface to the transducer via pieces of cannulas of a relatively wide bore A thinner and longer silastic tube carried the saline from the pump The lightness and flexibility of the tubes were necessary for the stability of the cup on the cornea The tube for the pressure recording was wide enough to allow an adequate recording of pulse amplitudes (Fig 5 middle and bottom)

In vitro experiments were made at room temperature on eyes from cadavers which were kept at 0–5°C (Celcius) in a moist atmosphere until the run of the experiments 15 to 42 h after death There was no correlation between the recorded data and time elapsed after death nor were the data influenced by removal of the corneal epithelium These observations conform with those made by Goldmann & Schmidt (1957 1961) in studies on applanation tonometry and were also investigated in connection with the present method since the epithelium of some of the cadaver eyes was loosened and had to be removed so that the measurements could be carried out on a smooth well preserved Bowman's membrane The experimental eye rested on cotton pads in a glass

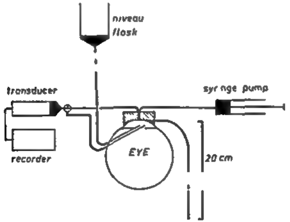

Fig 4

A sketch of the experimental set up for studying eyes of cadavers The applanating suction cup adheres to the cornea due to the siphon effect created by a hanging tube reaching 20 cm below the level of the eye A syringe pump delivering four milliliters of balanced isotonic salt solution per hour maintains an interspace between applanating and applanated surface A three way stop cock on the pressure transducer establishes the connection with either the anterior chamber of the eye or the fluid of the inter space The niveau flask allows an adjustment of the pressure in the anterior chamber The calibration flask for the transducer is not included

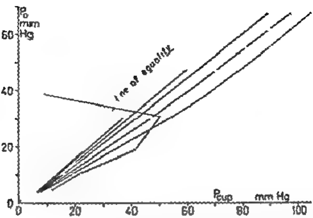

Fig 3

The relationships on the same eye of a human cadaver between central cup pressure (P_{cup} abscissa) and intraocular pressure (P_o ordinate) when using seven increasing values of depths of the same cup (Fig 1 C) Each new adjustment was obtained by unscrewing the central part 90 degrees corresponding to an increment in depth of cup of 0 125 mm The cup adjustment of the top (shortest) line was 5 6 that of the second line from the top was 5 725 etc The suction pressure was 15 mmHg and the inflow of balanced salt solution four ml per hour

funnel and the anterior chamber was connected to the pressure transducer as well as to a niveau flask via two thin needles both inserted from behind through the sclera and through the pupil (Fig 2) A three way stop cock on the transducer established the connection with either the disc of saline in the interspace (*giving* P_{cup}) or with the anterior chamber (P_o)

Results of in vitro experiments

1) Fig 3 shows the *correlation between* P_o *and* P_{cup} with different adjustments of the depth of the cup pictured in Fig 1 C measured on the same eye Each line is the result of one up down run The selected initial adjustment was called 5 6 this being the total height of the cup in millimeter measured with a slide gauge The pitch of the screw thread was 0 5 mm therefore the next adjustment when turning the central part 90 degrees counter clockwise was 5 6 + (0 5/4) = 5 725 mm and the next one 5 85 etc It may be observed in Fig 3 (legend) that the closer the adjustment is to the initial position (5 6) the closer the correlation line is to the line of equality The good linearity of the upper curves is representative for the remaining 13 eyes Thus when the coefficient of correlation (r method of least squares) was calculated for each line the

averages for all these coefficients for the adjustments 5 6 5 ı25 and 5 85 were as high as 0 99985 0 99988 and 0 99989 respectively At the 5 6 adjustment the applanated area is largest and therefore the cup falls off at a relatively low pressure (see Principle) Accordingly the upper experimental line in Fig 3 stops at the lowest pressure the second line from top stops at a somewhat higher pressure etc (the same was true for the remainder of the eyes Table I last column) At the smallest applanated areas the P_o P_{cup} relationships become non linear and useless

In Fig 4 all the paired measurements of P_o and P $_p$ made with adjustment 5 ı25 on 10 consecutive eyes are plotted The coefficient of correlation of the pooled data is somewhat smaller than that for a single up down run but ■

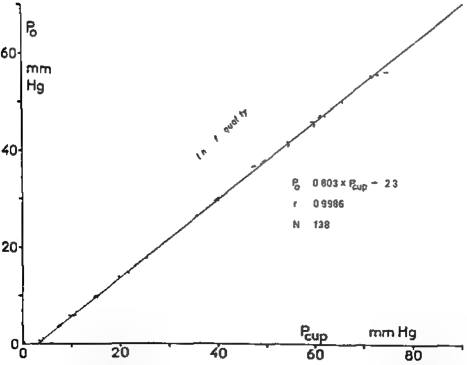

Fig 4

All the comparisons (138) between central cup pressure ($P_{c\ p}$ abscissa) and intraocular pressure (P ordinate) in 10 eyes of human cadavers with the same adjustment (5 ı95) of the cup (Γ g 1 C) The suction pressure was 15 mmHg and the inflow of balanced salt solution four ml per hour

Table I

Relationship between cup pressure (P_{cup}) and intraocular pressure (P_o) in 14 eyes of human cadavers

Adjust ment of cup	Relationships	r	N	No of eyes	Allowing mea surements of P_o up to approx (range)
5 6	$P_o = 0\ 84 \times P_{c\ p} - 2\ 1$ (mmHg)	0 9991	143	13	40 mmHg (18–50)
5 725	$P_o = 0\ 80 \times P_{cup} - 2\ 3$ (mmHg)	0 9986	133	10	50 mmHg (30–68)
5 85	$P_o = 0\ 74 \times P_{cup} - 1\ 5$ (mmHg)	0 984	74	5	60 mmHg (47–68)

* The pressures of the eyes were not raised beyond 68 mmHg

still good Measurements with the three lower adjustments gave the data of Table I The pressures at which the cup falls off (last column) are determined under the stable conditions which experimentation on eyes of cadavers provides It is the author s impression that these pressures are somewhat reduced when measuring on the pulsating and moving *in vivo* eyes

2) The effect of *changing the suction pressure* was checked in four eyes by raising or lowering the opening of the hanging silastic tube Variations between 11 and 24 cm of water (8–18 mmHg) affected P_{cup} with at most 0 5 mmHg as long as the suction was sufficient to stabilize the cup on the cornea

3) The effect of *changing the rate of inflow* of saline was also small (tested in three eyes) A variation between 0 4 and 20 ml per h caused a change of maximally 0 5 mmHg around the P_{cup} values obtained with the usual flow of four ml per h

4) During four to six *hours of experimentation* with an eye the correlation lines did not shift measurably

Results of in vivo experiments

Continuous recordings on 15 eyes of 15 patients with intraocular pressures up to 30 mmHg have been performed The eye was kept open with a lid speculum after the administration of oxybuprocaine solution (0 4 per cent) The patient lay on a couch and was instructed to fixate a point in the ceiling while the

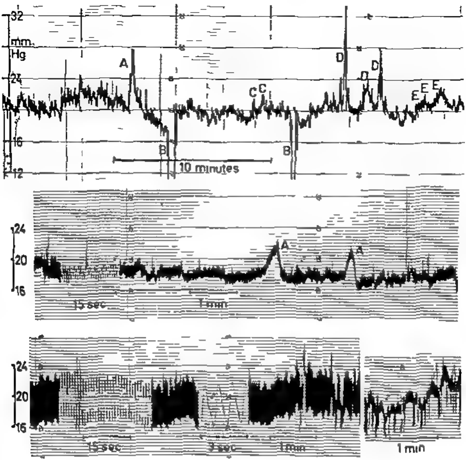

Fig 5

Recordings on eyes from four patients Ordinates cup pressure (P_{cup})

Top A part of a continuous recording lasting one hour The pressure transducer was damped by using narrow connections to the applanating suction cup (Fig 1 B) A spontaneous oscillation B check on zero of pressure transducer C the patient is talking D Valsalva maneuver E the patient is moving on the bed and talking Perkins applanation tonometry before the recording gave 18 mmHg

Middle An undamped recording with the cup pictured in Fig 1 C Adjustment 5 725 A spontaneous oscillation Perkins tonometry before the recording gave 13 mmHg

Bottom Undamped recordings with the cup pictured in Fig 1 C on two patients Perkins tonometry gave 17 mmHg (left) and 16 mmHg (right) before the recordings Cup adjustments 5 725 The patient with the many sharp falls in the pressure (right) had many cardiac extrasystoles The suction pressure was 15 mmHg and the inflow of balanced salt solution four ml *per hour*

cup was inserted The cup was held above the eye while an isotonic salt solution was injected into the free end of the hanging tube When all air bubbles had been removed from the tube and most of the cup was filled with fluid the cup was placed on the cornea and the cannula removed from the free end Now suction took over and the cup became stable on the cornea During the positioning of the cup a slow stream of saline entered the cup from the calibration flask for the transducer in order to prevent air bubbles from slipping into the pressure recording tube

Recordings lasting up to one hour have been made (Fig 5) The patients felt no discomfort during or after the measurement The corneae were coloured with fluorescein and were examined in the slit lamp before and after the recordings A staining of the corneal epithelium similar to the trauma made by readings with an applanation tonometer were sometimes noticed after the recording no major abrations of the epithelium have been observed The dynamic response of the system is excellent In most cases the pressures were also read with a Perkins applanation tonometer before the recording These values seem to be related to the cup pressure in good agreement with the calibration curves made on the eyes of cadavers however the material is still too small to warrent any conclusions

Experiments on Rabbit Eyes

Ten eyes freshly enucleated under barbiturate anaesthesia were tested with the cup depicted in Fig 1 B and the method shown in Fig 2 The suction pressure was however 10 mmHg The diameter of the applanated area of the cornea was estimated to approximately 4 5 mm by slit lamp inspection (see above) The rabbits weighed between 3 8 and 4 4 kg The line of correlation of the pooled data was

$P = 0\,94 \quad P_{cup} - 0\,1$ (mmHg) with a coefficient of correlation
$r = 0\,9996$ (number of comparisons 129)

The findings that the slope of the line as well as the coefficient of correlation are closer to 1 0 than the corresponding figures for the human cadaver eyes probably reflect the fact that the rabbit cornea is closer to an ideal membrane (Fig 1 A) than the human cornea it is thinner and it lacks Bowman s membrane (Goldmann & Schmidt 1961) The effect on P_{cup} of changing the suction pressure or the rate of saline infusion at a certain P_o was less than with human eyes (checked in six and eight eyes respectively)

Discussion

The measurements with the applanating suction cup compare favourably with those obtained with the applanation tonometer of Goldmann Goldmann & Schmidt (1961) found a coefficient of correlation (r) of 0 99 when comparing tonometer readings with intraocular pressures on eyes of human cadavers This value resembles the two upper r values shown in Table I With adjustment 5 85 of the cup (Table I bottom line) the r value is somewhat lower

On the same eye the correlation is equally good with the three lower adjust ments of the cup (r = 0 9999 see results) On a particular eye relative values of the intraocular pressure can thus be measured with the same accuracy at all three adjustments but in order to obtain absolute pressures the recorder must be calibrated according to the correlation line corresponding to the adjustment of the cup

The reason why the applanating suction cup overestimates the intraocular pressure is that the pressure in the central interspace (P_p) in addition to balancing the intraocular pressure must bend the cornea The reason why such a calibration factor apparently does not enter into consideration when the Goldmann applanation tonometer is used is that the effect of the corneal rigidity in this method is counteracted by the capillary attractive force of the coloured fluid meniscus (as emphasized by Goldmann & Schmidt 1961) In recent years however it has been demonstrated that in applanation tonometry the two forces do not always neutralize each other the corneal thickness and consequently the corneal rigidity may vary and give rise to errors of a few millimeters of mercury (Ehlers et al 1975) A similar error probably applies to the applanating suction cup method

When part of the cornea is applanated by the cup a volume of displaced aqueous must be accommodated within other parts of the coats of the eye The corresponding stretching of these will be accompanied by an increase in intra ocular pressure but with time the pressure will return to the preceding level since a raised intraocular pressure will keep the outflow of aqueous elevated above its equilibrium value Obviously this argument presupposes that the deformation of the cornea does not trigger reflexes of significance for the intraocular pressure regulation or act mechanically on the outflow or inflow system (cf Moses 1975) In one of the experiments with a cadaver eye mo mentarily disconnected from the niveau flask the cup was suddenly put on or removed at different levels of the intraocular pressure and the effect of this procedure was recorded At an intraocular pressure of around 20 mmHg a change of 3–4 mmHg (up or down) was observed (corresponding to a calcu lated applanation area of 4 6 to 4 9 mm in diameter assuming that a deforma

tion occurs only corresponding to the applanated area) 3–4 mmHg is the acute change in the pressure of the living eye to be expected from a cup induced distorsion Furthermore the time integrated Friedenwald law (Davanger & Holter 1967) teaches us that with a normal conductance of aqueous outflow it should take about 10 min for the pressure to return to the equilibrium value So in the living eye if no reflexes are triggered and if the outflow and inflow systems are uninfluenced by the distorsion of the cornea the corrected recorded cup pressure after approximately 10 min should be comparable to the pressure measured immediately before with an applanation tonometer Experimental evidences give the impression that this holds true

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References

Davanger M & Holter O (1967) Intraocular pressure in non equilibrium states *Acta ophthal (Kbh) 45* 510–524

Durham D G Bigliano R P & Masino J A (1965) Pneumatic applanation tonometer *Trans amer Acad Ophthal Otolaryng 69* 1029–47

Ehlers N Bramsen T & Sperling S (1975) Applanation tonometry and central corneal thickness *Acta ophthal (Kbh) 53* 34–43

Goldmann H & Schmidt Th (1957) Über Applanationstonometrie *Ophthalmologica 134* 221–242

Goldmann H & Schmidt Th (1961) Weiterer Beitrag zur Applanationstonometrie *Ophthalmologica 141* 441–456 Table I

Greene M E & Gilman B G (1974) Intraocular pressure measurement with instrumented contact lenses *Invest Ophthal 13* 299–302

Maurice D M (1958) A recording tonometer *Brit J Ophthal 42* 321–335

Moses R A (1975) *Adler's Physiology of the Eye* pp 191–192 Sixth ed Mosby St Louis

Nissen O I Kjer P & Olsen L (1976) A comparison between an acetazolamide test and weight tonography in pathological and apathological circulation of the aqueous humor *Invest Ophthal 15* 844–848

Ohnesorge F K Soyka H Soyka H & Zwieten P A van (1968) Continuous determination of intraocular pressure in the rat *Exp Eye Res 7* 70–74

Stepanik J (1976) Das Mackay Marg Tonometer VII Kontinuierliches Registrieren des Augendruckes I *Graefes Arch klin exp Ophthal 198* 171–177

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MODEL COMPUTATION OF THE EFFECT OF ARBITRARY VARIATIONS IN AQUEOUS INFLOW OUTFLOW CONDUCTANCE OCULAR RIGIDITY AND EPISCLERAL VEIN PRESSURE ON OCULAR PRESSURE

BY

OLE I NISSEN

Model calculations of the time course of the intraocular pressure are performed in cases where the four determinants mentioned in the title vary singly or simultaneously according to specified time functions As sumptions are 1) that the outflow of the aqueous humour is proportional to the driving pressure and 2) that the intraocular pressure and volume are related to each other as described by Friedenwald The mathematical solution is numerical and involves the repetition of the same calculatory step process It is rendered probable that the maximal inhibitory effect of acetazolamide on the secretion of aqueous humour is reached in less than one minute after the drug has reached the receptors A programmable calculator with 224 storage locations is used the programs are given.

Key words acetazolamide – aqueous secretion – computer program – conductance (facility) of aqueous outflow – episcleral vein pressure – Friedenwald s law – intraocular pressure – mathematical model – ocular rigidity

The dynamic intraocular pressure is assumed to be determined by the following four parameters inflow rate of aqueous humour conductance of the outflow channels of aqueous humour ocular rigidity and episcleral vein pressure the present method makes it possible to evaluate responses in the intraocular pres

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sure (e.g. to drugs) in terms of well defined mathematical models in which these parameters vary as arbitrary functions of time. Recently developed instruments allow good continuous recordings of the intraocular pressure (Nissen 1977) and the easy access to programmable calculators has made it practicable to perform the model calculations on the recorded data.

The two basic elements of the model are well known from texts on ocular hydrodynamics. They are the Friedenwald (1937) relationship between pressure and volume of the eye, and the assumption that the outflow rate of aqueous humour is proportional to the driving pressure (i.e. intraocular pressure minus episcleral vein pressure). On this basis Davanger & Holter (1967) evaluated the time integrated Friedenwald law that describes the course of the ocular pressure towards its steady state value after a transient disturbance of the ocular hydrodynamics.

What is new in the present context is the use of a numerical procedure involving the repeated application of the same calculatory step process. This type of solution is ideally suited to programmable computers in virtue of their ability to perform 'loops', and it allows the independent variables to vary according to rather complex time functions. An important point is that the error of the approximated result is calculable and may be reduced as required.

After a description of the principle of the calculation, two examples will be presented.

Symbols

Δt (min) a small time interval

P_t (mmHg) intraocular pressure at time t

$F_{in,t}$ (μl min^{-1}) rate of aqueous inflow at time t

C_t (μl min^{-1} mmHg^{-1}) conductance of aqueous outflow ('outflow facility') at time t

E_t coefficient of ocular rigidity at time t (natural logarithms) defined by Friedenwald's (1937) pressure volume relation of the eye. Average values for this coefficient in the pressure range 15–35 mmHg lie between 0.03 and 0.05 (Ytteborg 1960, Langham & Eisenlohr 1963, Friedenwald 1954, through Duke-Elder 1968)

$P_{v,t}$ (mmHg) episcleral vein pressure at time t

$P_{e,t}$ (mmHg) the equilibrium pressure with an inflow rate of $F_{in,t}$, an outflow conductance of C_t and an episcleral vein pressure of $P_{v,t}$

$P_{t,E}$ (mmHg) intraocular pressure at time t corrected for a step change in the ocular rigidity

Principle

A non-equilibrium state in the ocular hydrodynamics of the type treated by Davanger & Holter (1967) might follow from e.g. an injection of a volume of fluid into the eye, or a sudden shift in the rate of aqueous secretion. In such

a state the intraocular pressure at time t may be calculated from the pressure immediately after the step disturbance (P) and the final equilibrium pressure (P_{eq}) if the determinants of the latter (assumed to be F_{in} C and P_v) are constant during the change of pressure towards its equilibrium value E and C must be known

$$P_t = P_0 \quad P_{eq} - \left[P \; -(P_0 - P_{q}) \quad e^{-(E \quad C \quad P_q \quad t)} \right] \tag{1}$$

This is the equation we will apply in the calculatory step process

The initial situation in an eye in a steady hydrodynamic state The intraocular pressure is P and the four independent variables are $F_{in\,0}$ C E_0 and $P_{v\,0}$ At time zero these four parameters begin to change according to certain time functions (e g those chosen in example 2) We divide the time from zero in short intervals of equal lengths Δt Within each interval we assume that the four parameters or independent variables are constant and given by the four specified time functions at the end of the interval Thus in the interval lasting from t Δt to t they are assumed to be $F_{in\,t}$ C_t E_t and $P_{v\,t}$ The intraocular pressure at the end of the interval is calculated according to equation 1 (eq 1)

$$P_t = P_{t\,\Delta t} \quad P_{q(t)} - \left[P_{t\,\Delta t} - (P_{t\,\Delta t} - P_{q(t)}) \quad e^{-(E_t \quad C_t \quad P_{eq(t)} \quad \Delta t)} \right] \tag{2}$$

where $P_{eq(t)}$ is defined by the following equation expressing that inflow equals outflow in a steady state

$$F_{\;t} = C_t \quad (P_{q(t)} - P_{\;t}) \text{ or}$$
$$P_{q(t)} = (F_{n\,t}/C_t) + P_{v\,t} \tag{3}$$

At the start of the first computer run the content of the time register is increased from zero to Δt Then the values of $F_{\;\Delta t}$ $C_{\Delta t}$ $E_{\Delta t}$ and $P_{\;\Delta t}$ are computed according to the programmed time functions and stored in their respective registers (the effect of step changes in E is actually more complicated than indicated here see below) $P_{q(\Delta t)}$ is then calculated from eq 3 and finally $P_{\Delta t}$ can be determined from eq 2 and stored After this the computer loops back adds another Δt to the content of the time register and calculates a new set of values of the four determinants From these and the $P_{\Delta t}$ obtained in the first run $P_{\;\Delta t}$ is calculated In general the P_t calculated in the computer run number $t/\Delta t$ becomes $P_{t\,\Delta t}$ in the next run

P_t may equally well be calculated only from the three independent parameters of eq 2 $P_{eq\,t)}$ C_t and E_t This principle is used in example 1

In the programs of examples 1 and 2 the computer was instructed to print the value of P_t whenever the content of the time register (t) was a whole number (i e every minute) The calculation process continues until it is stopped either manually or by certain stored limiting conditions (example 1)

The fact that a step change in *the rigidity of the coats* of the eye (the ocular rigidity) must produce a step change in the intraocular pressure makes a correction of the latter necessary at the start of each new Δt interval

The Friedenwald law says

$$E_1 \Delta V = \ln P_{b1} - \ln P_{a1} \tag{4}$$

where ΔV is a volume added to an eye with an ocular rigidity of E_1, P_{a1} is the pressure before and P_{b1} the pressure after the addition of ΔV

If E_1 in this eye changes to E_o and we add the same volume we have similarly

$$E_o \Delta V = \ln P_{bo} - \ln P_{ao} \tag{5}$$

(4) combined with (5) results in

$$\frac{E_1}{E_o} = \frac{\ln P_{b1} - \ln P_{a1}}{\ln P_{bo} - \ln P_{ao}} \tag{6}$$

It is obvious from this equation that we have to specify the values of P_{a1} and P_{ao} if we shall calculate P_{bo} from P_{b1}, E_1 and E_o. To simplify the calculations we decide that both the P_a values are 1 mmHg in the present eye model We then have

$$P_{bo} = e^{(E_o/E_1)\ \ln P_{b1}} = P_{b1}^{(E_o/E_1)} \tag{7}$$

It may be seen that this decision implies that with an intraocular pressure of 1 mmHg there is no effect of a change in the ocular rigidity We now return to the original problem At the time $t-\Delta t$ when E changes from $E_{t-\Delta t}$ to E_t the intraocular pressure will immediately step from $P_{t-\Delta t}$ to a value $P_{t-\Delta t\ F}$ which we define by eq 7

$$P_{t-\Delta t\ F} = P_{t-\Delta t}^{(E_t/E_{t-\Delta t})} \tag{8}$$

$P_{t-\Delta t\ E}$ is computed by the machine from eq 8 following the calculation of E_t. In summary when $E_{t-\Delta t}$ changes to E_t at the start of an interval E_t shall not only replace $E_{t-\Delta t}$ in the exponent of e (of eq 2) but it will immediately alter $P_{t-\Delta t}$ to a new value $P_{t-\Delta t\ E}$ which has to replace $P_{t-\Delta t}$ (of eq 2 cf the program of example 9)

The smaller the Δt the more exact the time course of the determined intraocular pressure An exact measure of *the maximal error* of the result at a certain value of Δt may be obtained in the following way (assuming for the purpose of simplicity that only F_n varies)

In Fig 1 (left) we have depicted F_{nt} as a linear function of time In the iterative calculation we let F_n move along this line in steps of Δt min which are represented by the full drawn rectangular falls E g in the second interval (from 2½ to 5 min) a value for F_n is used which should actually be reached only after 5 min In other words the chosen rate of aqueous production is too low for most of the time Consequently the intraocular pressure (Fig 1 right) will also be determined at too low a rate However we might also have calculated the course of P_t so that it was determined at too high a rate (indicated by the dotted rectangular falls) With respect to the calculation by eq 9 this would merely require that we inserted $F_{n\,t+\Delta t}$ instead of $F_{n\,t}$ in eq 3 The difference between P_t determined in the two ways represents the maximal error at the chosen magnitude of Δt This was found less than 0 1 per cent of P_t for $\Delta t = 0\ 01$ min in the example illustrated in Fig 1 The time of the computation at this level of accuracy was approximately four hours using a Texas SR 52 calculator

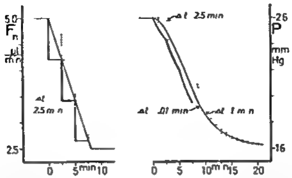

Fig 1

Computation of the course of the intraocular pressure from a known variation of the inflow of aqueous humour F_{in} (C = 0.25, E = 0.0495, P_v = 6 mmHg). To the left the falling and later horizontal line pictures the true variation of $F_{in,t}$ with time. To the right the calculated variation in the intraocular pressure with time for different Δt values is depicted. When Δt is reduced the two step curves (left) representing the approximated variation in $F_{in,t}$ will fuse as will the two calculated pressure curves. The full drawn curve on the right side is actually the result of a computation with a Δt of 0.01 min and may be regarded as the correct change of P with time (maximal error on P_t less than 0.1 per cent).

If in addition the three other independent variables C_t, E_t and $P_{v,t}$ vary a similar argument can be applied. P_t may still be calculated in the two ways by using for the Δt intervals the F_t, C, E and P_v values applying to the start or the end of the intervals; the difference again gives the maximal error.

No doubt the calculator can be pressed beyond its capabilities, e.g. by letting the step process repeat itself so many times that the accumulating error of each iteration will eventually be perceptible, or by letting the independent variables change by such small Δt steps that some significant figures are lost in the intermediate calculations (the Texas calculator works with 13 digits, some larger computers may use 25 digits). In each case the user has to make sure that the computation fulfills the demands for accuracy.

The use of the method is illustrated by two examples.

Example 1

Discussion of the postulate that acetazolamide given as an intravenous injection causes a step fall in the rate of aqueous secretion. The immediate response of the intraocular pressure to intravenous acetazolamide is a relatively steep fall starting abruptly 2–4 min after the injection (at the arrow in Fig 2); the pressure curve gradually flattens out and reaches an equilibrium value. Nissen & Hoppe (1974) postulated that this event was the result of a step decrease in the rate of aqueous inflow to a new constant level (occurring at the arrow in Fig 2)

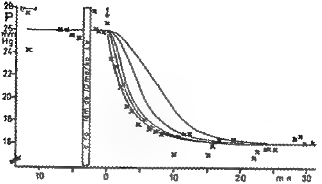

Fig 2

Illustration to example 1 Readings with a Goldmann applanation tonometer (crosses) before and after an intravenous injection of acetazolamide to a patient with an intra ocular hypertension The smooth curves are calculated on the basis of an outflow conductance (facility) of 0 3 a normal ocular rigidity (E) of 0 0495 and constancy of the episcleral vein pressure The curve to the far left is calculated assuming a step fall in the production rate of aqueous humour (or rather in $P_{eq(t)}$ see the text) The other curves are calculated assuming linear falls in the production rate lasting (from the left) 1 2 5 and 10 min respectively (Error on P_t less than 0 1 per cent) Abscissa time in minutes ordinate intraocular pressure in mmHg

with constant outflow conductance episcleral vein pressure and ocular rigidity during the pressure fall If that is the case we have a non equilibrium state in ocular hydrodynamics of the type treated by Davanger & Holter (1967) Hypothetical reference curves can then be calculated from equation 1 assuming different values for the outflow conductance a chosen (normal) value for the ocular rigidity (E = 0 0495) and a constancy of the episcleral vein pressure P of eq 1 is then the preinjection pressure of the experiment (26 mmHg in Fig 2) and P_q the postinjection steady state pressure (16 mmHg in Fig 2) Among these reference curves calculated from various values of the outflow conductance (C) the one obtained for C = 0 3 fits the experimental pressure points reasonably well (the full drawn curve to the far left)

Accepting this as an approximate value of the outflow conductance we may *now* use the new numerical method to test the assumption of a step fall in the aqueous secretion rate The experimental pressure points are compared with another set of pressure decay curves calculated from C = 0 3 and a *non instantaneous* fall in the aqueous secretion rate (and a constant episcleral vein pressure and ocular rigidity) These new curves are calculated in the following way

If the fall in the aqueous inflow rate to a new level takes a certain time the fall in the equilibrium pressure ($P_{q(t)}$) will take the same time (eq 3 where

$C = 0.3$ and $P_{v,t}$ are constant) Consequently we let $P_{eq(t)}$ be the independent variable in the numerical calculation and choose an equation according to which it shall fall e g a simple linear equation

$$P_{eq(t)} = 26 - k \cdot t \tag{9}$$

and instruct the calculator to halt the fall when $P_{eq(t)}$ reaches 16 mmHg The constant k is selected so that the fall takes 1 2 5 or 10 min ($k = 10$ 5 2 and 1) the four decay curves are computed and appear to be S shaped as shown in Fig 2 (Sets of S shaped curves with C values of 0.5 and 0.7 were also calculated but are not shown their fit with the experimental data was found to be poor) The question is then Which of the five smooth curves looks most like our experimental curve?

In my opinion the zero and the one minute curve of Fig 2 (the two curves to the far left) can both be fitted reasonably well to the experimental points while the more pronounced S shape of the rest cannot This impression is confirmed by more than 100 acetazolamide tests an S shape of the type suggested by the four of the full drawn curves in Fig 2 is not the typical finding On the other hand it should be admitted that the low degree of S shape seen with a one minute fall in secretion is so difficult to detect in the experiment that the following conclusion seems tenable When acetazolamide is injected intravenously in a dose of 10 mg per kg body weight the fall in the rate of production of aqueous humour to a new level takes less than one minute

The following program was used

Program (Texas SR 52 with printer) LBL A CLR STO 13 RCL 02 PRT RCL 03 PRT RCL 04 PRT RCL 05 PRT RCL 01 STO 11 PAP PRT LBL A' CLR RCL 05 SUM 13 RCL 01 – RCL 13 × RCL 04 = STO 12 – RCL 02 = ifPOS B RCL 02 STO 12 LBL B RCL 12 × .0495 × RCL 03 = RCL 05 = INV LNX ÷ (STO – 1 + RCL 12 — RCL 11) × RCL 12 = STO 11 RCL 13 X↔t ifERR C RCL 11 PRT RCL 12 PRT RCL 13 PRT LBL C CLR RCL 11 – RCL 02 – .3 = INV ifPOS D A' LBL D RCL 02 PRT PAP PAP HLT

Procedure Store the preinjection pressure (P_0) in register 01 the postinjection steady state pressure (P_{eq}) in reg 02 the estimated outflow conductance (C) in reg 03 the constant (k) of eq 9 in reg 04 and Δt in reg 05 Press A The following is printed P_{eq} C k Δt P_0 P_1 $P_{eq(1)}$ 1 P_t $P_{eq(t)}$ t P_{eq} When P_t is nearer than 0.3 mmHg from P_{eq} the calculation halts Δt must be selected so that $1/\Delta t$ is a whole number

The remaining registers which are in use contain reg 11 P_t reg 12 $P_{eq(t)}$ reg 13 t

C may be estimated from sets of precalculated reference curves described earlier Nissen & Hoppe 1974 These reference curves (corresponding to a step fall in aqueous secretion) may also be obtained from this program by setting $k \geq (P_0 - P_{eq}) \div \Delta t$ Δt may be e g ½ or 1 min

Example 2

Model computation of the intraocular pressure in a dying patient We select rather arbitrarily the functions along which the four determinants of the intra ocular pressure change as

$$F_{n,t} = 5 \quad \cos(\pi \quad \frac{t}{25}) \qquad \text{with stop for further} \tag{10}$$

variation in $F_{n,t}$ when it reaches zero

$$C_t = 0.25 - 0.15 \quad \sin(\pi \quad \frac{t}{20}) \tag{11}$$

$$E_t = 0.75 \quad 0.0495 + \frac{0.25 \quad 0.0495}{1.2^t} \tag{12}$$

$$P_{v,t} = 6 + 6 \quad \sin(\pi \quad \frac{t}{24}) \tag{13}$$

The chosen time functions are based on the following reasoning a change in pupil size and/or ciliary muscle tone might explain the fall and later the rise in the outflow conductance a vasoconstriction might produce a fall in ocular rigidity be lessening the tissue tension a backward failure might produce a transient increase in the epi scleral vein pressure

The four top parts of Fig 3 show the resulting intraocular pressure variations when one determinant varies at a time and the others are kept constant at the initial values the bottom figure gives the result when the four variables work together Fig 3 illustrates among other things 1) A sine variation of C is followed after a lag of time by a variation in P which resembles a sine curve but is not strictly so because of the unlinearity between pressure and volume which is contained in the Friedenwald law (second illustration from top) 2) a permanent fall in the ocular rigidity produces only a transient fall in the intraocular pressure (third illustration from top) and 3) a significant pressure change due to a change in outflow conductance presupposes a well functioning secretory epithelium (compare the second illustration from top with the bottom illustration)

The curves of Fig 3 bottom were calculated by means of the following program

Program (Texas SR 52 with printer) LBL A CLR 96 STO 01 0495 STO 04 STO 1
O STO 15 LBL A CLR RCL 06 SUM 15 RCL 15 — 25 × π = cos 7 = ifpos B
LBL B STO 02 RCL 15 — 20 × π = sin × 15 +/– + 25 = STO 03 RCL 04 × 05 + ST
— 3 — 1 2 y^x RCL 15 = STO 13 RCL 01 y^x (RCL 13 — RCL 12) = STO 14 RC
15 — 24 × π sin 6 + 6 = STO 05 + RCL 02 — RCL 03 = STO 11 × RCL 13 ST
12 × RCL 03 RCL 05 = inv lnx — (STO = 1 + RCL 11 — RCL 14) × RCL 11
STO 01 RCL 15 Nf ifert A RCL 01 PRT RCL 02 PRT RCL 03 PRT RCL 12 PR
RCL 05 PRT RCL 1 PRT 1

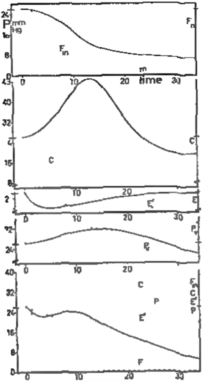

Fig 3

Illustration to example 2 The figures show (from top) the calculated variations of intraocular pressure (P full drawn curves) with time when the determinants of the pressure (dotted curves) vary singly (Nos *1 2 3* and *4*) and simultaneously (No *5*) Abscissa time in min Left ordinates intraocular pressure in mmHg Right ordinates from above inflow rate of aqueous humour outflow conductance (facility) ocular rigidity episcleral vein pressure and the four together Mark on the ordinates initial values (F =5 C_0=0 25 E =0 0495 P_v =6) The computations are based upon a Δt=0 01 min implying that the maximal error at any P is less than 0 2 per cent

Procedure Store Δt in register 06 ($1/\Delta t$ must be a whole number) Press A The following is printed P_1 F_1 C_1 E_1 P_{v1} 1 P_t F_t C_t E_t P_{vt} t The calculation continues until HLT is pressed The contents of the registers in use are 01 P_t 02 F_t 03 C_t 04 E_0 05 P_t 06 Δt 11 $P_{eq(t)}$ 1 $E_{t\Delta t}$ 13 E_t 14 P_{tE} 15 t The rad deg switch must be in the R position

References

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Example 2

Model computation of the intraocular pressure in a dying patient We select, rather arbitrarily the functions along which the four determinants of the intra ocular pressure change as

$$F_{in,t} = 5 \cdot \cos\left(\pi \cdot \frac{t}{25}\right) \quad \text{with stop for further} \tag{10}$$

variation in $F_{in,t}$ when it reaches zero

$$C_t = 0.25 - 0.15 \cdot \sin\left(\pi \cdot \frac{t}{20}\right) \tag{11}$$

$$E_t = 0.75 \cdot 0.0495 + \frac{0.25 \cdot 0.0495}{1.2^t} \tag{12}$$

$$P_{v,t} = 6 + 6 \cdot \sin\left(\pi \cdot \frac{t}{24}\right) \tag{13}$$

The chosen time functions are based on the following reasoning a change in pupil size and/or ciliary muscle tone might explain the fall and later the rise in the outflow conductance a vasoconstriction might produce a fall in ocular rigidity be lessening the tissue tension a backward failure might produce a transient increase in the epi scleral vein pressure

The four top parts of Fig 3 show the resulting intraocular pressure variations when one determinant varies at a time and the others are kept constant at the initial values the bottom figure gives the result when the four variables work together Fig 3 illustrates among other things 1) A sine variation of C is followed after a lag of time by a variation in P which resembles a sine curve but is not strictly so because of the unlinearity between pressure and volume which is contained in the Friedenwald law (second illustration from top) 2) a permanent fall in the ocular rigidity produces only a transient fall in the intraocular pressure (third illustration from top) and 3) a significant pressure change due to a change in outflow conductance presupposes a well functioning secretory epithelium (compare the second illustration from top with the bottom illustration)

The curves of Fig 3 bottom were calculated by means of the following program

Program (Texas SR 52 with printer) LBL A CLR 26 STO 01 0495 STO 04 STO 17 O STO 15 LBL A CLR RCL 06 SUM 15 RCL 15 — 25 × π = cos × 5 = ifpos B 0 LBL B STO 02 RCL 15 — 20 × π = sin × 15 +/− + 25 = STO 03 RCL 04 × 75 + STO — 3 — 1 2 y RCL 15 = STO 13 RCL 01 yˣ (RCL 13 — RCL 12) = STO 14 RCL 15 — 24 × π sin × 6 + 6 = STO 05 + RCL 02 — RCL 03 = STO 11 × RCL 13 STO 12 × RCL 03 RCL 05 = inv Int — (STO — 1 + RCL 11 — RCL 14) × RCL 11 STO 01 RCL 15 ... RCL 01 PRT RCL 02 PRT RCL 03 PRT RCL 17 PRT RCL 05 PRT RCL 1 PRT A

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MOVEMENT OF HORSERADISH PEROXIDASE IN THE CORNEA SCLERA AND THE ANTERIOR UVEA

BY

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The anterior chambers of rabbit monkey and human eyes were perfused with horseradish peroxidase The perfusion was started immediately after enucleation of the monkey and human eyes while the rabbit eyes were perfused *in situ* after the animals had been killed Comparative results were obtained after 1 h of perfusion and were mainly based on frozen sections Intensive staining was found in the Descemet s membrane the sclera and the iridial stroma considerably more than in the corneal stroma and in the ciliary body base In the vervet monkey and human eyes only traces of peroxidase reaction products were seen in the stroma of the ciliary body base The movement of the protein tracer from the anterior chamber into the corneal stroma is probably dependent upon vesicular transport across the corneal endothelium The Descemet s membrane was interpreted to be more porous than the corneal stroma A trans corneal and a corneo scleral movement appeared to be more efficient than the uveo scleral one at least in the vervet monkey and the human eyes

Key words permeability – horseradish peroxidase – cornea – iris – ciliary body – Descemet s membrane

Donn Kaye Mallet & Pappas (1961) and Kaye & Pappas (1962) demonstrated that the corneal endothelium was able to take up and transport such colloidal tracers as thorium dioxide saccharated iron oxide ferritine and haemoglobulin by means of vesicles The uptake of horseradish peroxidase by the corneal endo thelial cells was studied by Kaye Sibley & Hoefle (1973) The active vesicular transport of horseradish peroxidase across the corneal endothelium and the

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further permeation of this tracer up to the uttermost cell layer of the corneal epithelium was studied by Tønjum (1974a, b).

It has repeatedly been demonstrated that the capillaries of the ciliary and the iridial processes and of the choroid are leaky to a variety of proteins (Bill 1964, 1968; Shiose 1970; Smith 1971; Vegge 1971). By means of radioactive tracer technique Bill (1965) demonstrated that serum albumin, myoglobulin and immunoglobulins could be recovered in fairly large quantities in the sclera and the uvea after having been introduced into the anterior chamber of different species. This movement of the tracer was interpreted as taking place through the uveal tissues to the sclera, a uveo-scleral flow, and was regarded as a bulk flow along this route.

Pedersen & Tønjum (1975) showed, besides the leakiness of the capillaries of the ciliary and the iridial processes, that there existed a barrier at the base of the processes which inhibited the movement of horseradish peroxidase from the stroma of the processes to the stroma of the ciliary body.

The purpose of this paper is to present some observations on the gross distribution pattern of peroxidase reaction products in the rabbit, vervet monkey and human eyes after perfusion of the anterior chamber with this tracer enzyme.

Materials and Methods

In the present study the findings after perfusion of dead eyes are reported. Six eyes of albino rabbits weighing 3–3.5 kg were used. The animals were killed with an overdose of sodium pentobarbital and the anterior chambers of their eyes were perfused *in situ* for 30, 60 and 120 min. The four eyes of two vervet monkeys (Cercopithecus aethiops) were enucleated immediately after having been killed with a combination of phenycyclidine hydrochloride and ketamin hydrochloride and subsequent bleeding. One human eye of a female patient 56 years of age was removed under local anaesthesia because of a small melanoma in the posterior pole. Besides that, no gross pathology was detected by routine examination. The perfusion of the monkey and human eyes was started immediately after the enucleation and lasted for 60 min.

The horseradish peroxidase ('Sigma', type II) was used in a concentration of 2 mg per ml of Krebs-Ringer bicarbonate solution with glucose 5 mg per ml at pH 7.4. The intraocular pressure was kept at 20 mmHg. The experiments were performed at 25°C. A cannula of 27 gauge was introduced into the eyeball at the pars plana and pushed forward so that the tip of the cannula was located in the pupillary area. After completing the perfusion with the horseradish peroxidase solution, the eyes were opened broadly with a razorblade and prefixed in glutaraldehyde 2.5 % in 0.1 M phosphate buffer at pH 7.4 for 90 min.

Sectioning of the eyes was done meridionally and the slices included both cornea iris and ciliary body with the processes sclera and the choroid Sections of 40 μ were made with a freeze sectioner These tissue slices were incubated with diaminobenzidine and hydrogen peroxide in Tris HCl buffer for about 15 min and then rinsed throughly with distilled water

Slices of the eye of about 1 mm in thickness were also incubated *en bloc* with diaminobenzidine and hydrogen peroxide in Tris HCl buffer for 90 min These specimens were postfixed in osmium tetroxide for 1 h dehydrated in alchohol and embedded in Epon 812 Semithin and ultrathin sections were cut with a LKB microtome and examined with a light microscope or a Siemens Elmiscope I

Observations

a) Perfusion of the rabbit eyes

The frozen sections showed the gross distribution pattern of the horseradish peroxidase in the cornea the sclera the iris and the ciliary body after perfusion of the anterior chamber for different periods of time

After perfusion for *30 min* the periphery of the cornea was stained throughout its full thickness to the epithelium whereas in the central area the staining tapered off towards the anterior surface and peroxidase reaction products (PORP) could not be demonstrated between the epithelial cells A striking finding was the intensive staining of the Descemet s membrane There was some staining of the anterior part of the sclera and the iris stroma considerably less in the base of the ciliary body and the iridial and the ciliary processes were un tained

After *60 min* of perfusion PORP were present between the epithelial cells also in the central area of the cornea but the stromal staining became reduced in intensity from the posterior towards the anterior layers There was also a more intensive staining in the periphery as compared to the thinner central part of the cornea and it reached uninterrupted backwards into the sclera cor responding to the pars plana Although less than in the overlying sclera there was some staining of the ciliary body base and it extended into the stroma of the proximal parts of the ciliary and the iridial processes and backwards it reached into the choroid (Fig 1)

After *120 min* of perfusion all parts were more intensively stained The Descemet s membrane was still considerably darker than the corneal stroma The stroma of the ciliary body base was not as dark as the overlying sclera Staining was present in the stroma of the ciliary and the iridial processes almost to the tips and in the sclera and the choroid backwards to the poste rior pole

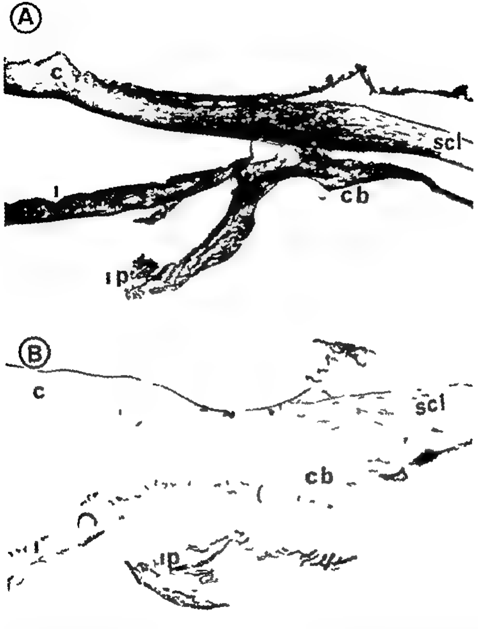

Fig 1

A Meridional frozen section 40 μ in thickness of a rabbit eye perfused with horseradish peroxidase in the anterior chamber for 60 min The gross distribution of peroxidase reaction products is demonstrated B Frozen section of a non perfused control rabbit eye Endogenous staining of intravascular red blood cells c cornea scl sclera i iris ip iridial process cb ciliary body ×40

b) Perfusion of monkey eyes

In the restricted number of monkey eyes available the duration of the perfusion was set to 60 min but otherwise the eyes were processed in the same manner as the rabbit eyes The frozen sections showed that the stroma of the central part of the cornea was less intensively stained than that of the limbal area Again the Descemet s membrane was more intensively stained than the stroma It was also noticeable th it the Descemet s membrane in the monkey eye became much thicker towards the periphery and the whole extent of this structure including Schwalbe s line had the same staining property The epithelium re mained pale as compared to the stroma but Epon embedded sections revealed PORP in the intercellular spaces The stroma of the ciliary body was only slightly stained and this was confined to the anterior part neighbouring the anterior chamber This was different from the more intensive staining of the ciliary body of the rabbit eyes after the same perfusion time

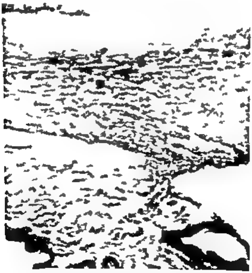

Fig 2

Frozen section of a human eye perfused with horseradish peroxidase for 60 min The staining of the cornea appears to continue into the sclera with a sharp border to the unstained part which may serve as a control Note the distinctly less staining in the stroma of the ciliary body than in the sclera with a sharp border between these structures x 70

The anterior chamber was perfused and the tracer moved from there to the neighbouring tissues One conspicuous finding was the intensive staining of the Descemet s membrane and also of the corneal stroma while the endothelium was pale and contained dark dots in the cytoplasma This is in accordance with the previous finding (Tonjum 1974a) that considerable amounts of horseradish peroxidase is transported across the endothelium by means of endocytotic vesicles the endothelial lining being intact The intercellular junctional complexes are assumed to be gap junctions It appears that only small amounts of this tracer move along these intercellular spaces The Descemet s membrane seems to be a porous structure with a large protein available space allowing peroxidase to enter into it and to harbour large amounts of the reaction products Even though the Descemet s membrane is mechanically very strong it is a highly permeable structure

The tracer molecules also move readily into the corneal stroma and subsequently into the sclera since there was a continuous staining from the corneal stroma into the sclera There is also a possibility that some molecules could have permeated from the drainage channels in the limbal region into these tissues There was a definite border between the pale anterior part of the ciliary body and the overlying dark sclera This was particularly so in the monkey and the human eyes In the rabbit eyes the tracer could be followed part of the way into the ciliary and the iridial processes while this could not be done in the monkey and the human eyes after 60 min Pedersen & Tonjum (1975) demonstrated a barrier against movement of peroxidase at the base of the processes in the living rabbit eyes In the present dead rabbit eyes peroxidase is inhibited but not completely prevented from entering the processes However the pressure gradients are different from those in the living eyes Only slight amounts of the tracer enzyme seemed to have entered the ciliary body stroma of the monkey and human eyes Some staining was due to the endogenous peroxidase of the plain muscle fibers

Thus the tracer seems to have moved along a *transcorneal* and a *corneo scleral* route The first step is most likely to a major extent an active transport across the endothelium by means of endocytotic vesicles This movement has only a limited correlation to movement of water and small molecules It is dependent upon the ability of molecules and particulate matters to stimulate endocytotic activity and transport and may be in agreement with a pressure independent movement In the vervet monkey and human eyes therefore the present technique indicates that the transcorneal and corneo scleral route is more efficient than the uveo scleral one

These observations may be related to those obtained by Allansmith Whitney McClellan & Newman (1973) by means of immunofluorescence technique on

human eyes and elusion of the tissues and subsequent precipitation of the different immunoglobulins. Their studies revealed relatively high concentrations in the stroma of the cornea and in the sclera, but only little in the stroma of the ciliary body, which seems to be consistent with the distribution pattern of PORP in the present study. Because of autofluorescence of the Descemet's membrane they were not able to differentiate between the concentrations in this structure and the corneal stroma.

The intensive staining of the iridial stroma is in accordance with previous studies showing that this tissue is porous and permeable to a series of substances such as dextranes (Gregersen 1958, 1959).

References

Allansmith M. R., Whitney C. R., McClellan B. H. & Newman L. P. (1973) Immunoglobulins in the human eye. *Arch. Ophthal. (Chicago)* 89, 36–45.

Bill A. (1964) The albumin exchange in the rabbit eye. *Acta physiol. scand.* 60, 18–29.

Bill A. (1965) The protein exchange in the eye with aspects on conventional and uveoscleral bulk drainage of aqueous humour in primates. *Eye Structure* II. Symp. Ed. by Rohen J. W. Schattauer Verlag, Stuttgart, 313–320.

Bill A. (1968) Capillary permeability to and extravascular dynamics of myoglobulin, albumin and gammaglobulin in the uvea. *Acta physiol. scand.* 73, 204–219.

Donn A., Kaye G. I., Mallet N. M. & Pappas G. D. (1961) Pinocytosis in rabbit corneal endothelium. *Arch. Ophthal. (Chicago)* 66, 835–845.

Gregersen E. (1958) The tissue spaces in the human iris and their communication with the anterior chamber by way of the iridic crypts. *Acta ophthal. (Kbh.)* 36, 819–828.

Gregersen E. (1959) *Elimination of high and low molecular dextran fractions from the anterior chamber and iris stroma of rabbit eyes. Acta ophthal. (Kbh.)* 37, 35–38.

Kaye G. I. & Pappas G. D. (1962) Studies on the cornea. I. The fine structure of the rabbit cornea and the uptake and transport of colloidal particles by the cornea in vivo. *J. Cell Biol.* 12, 457–479.

Kaye G. I., Sibley R. C. & Hoefle F. [illegible] (1973) Recent studies on the nature and function of the corneal endothelial barrier. *Exp. Eye Res.* 15, 585–613.

Pedersen O. Ø. & Tønjum A. M. (19[illegible]) Protein diffusion barriers in the anterior uvea of the rabbit eye. *Acta ophthal. (Kbh.)* 5[illegible], 6[illegible]–[illegible]6.

Shiose Y. (1970) *Electron microscopic studies on blood retinal and blood aqueous barriers. Jap. J. Ophthal.* 14, [illegible]3–87.

Smith [illegible] S. (1971) *Ultrastructural studies of the blood aqueous barrier. I. Transport of an electron-dense tracer in the iris and ciliary body of the mouse. Amer. J. Ophthal.* 7[illegible], 1066–10[illegible].

Tønjum A. M. (1974a) Vesicular transport of horseradish peroxidase across the rabbit corneal endothelium. *Acta ophthal. (Kbh.)* 52, 647–643.

Tønjum A. M. (1974b) Permeability of horseradish peroxidase in the rabbit corneal epithelium. *Acta ophthal. (Kbh.)* 52, 6[illegible]0–658.

Vegge T (1971) An epithelial blood aqueous barrier to horseradish peroxidase in the ciliary processes of the vervet monkey (Cercopithecus aethiops) *Z Zellforsch 114* 309–320

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THE PERMEABILITY OF THE HUMAN CILIARY AND IRIDIAL EPITHELIUM TO HORSERADISH PEROXIDASE

An In Vitro Study

BY

ASBJØRN M TØNJUM and OLAV ØYVIND PEDERSEN

The permeability of the human ciliary epithelium to horseradish peroxidase (PO) has been studied *in vitro* with the electron microscope Ciliary body and iris specimens were obtained from freshly enucleated eyes PO was applied at the stromal side of the epithelium and was left for 120 min The movement of PO through the intercellular spaces of the human ciliary epithelium was blocked apically in the lateral intercellular spaces of the non pigmented epithelial cells indicating that these cells are girdled by *zonulae occludentes*

In the iridial epithelium the same distribution pattern of peroxidase reaction products (PORP) was found i e the progression of PO was blocked apically in the lateral intercellular spaces of the posterior epithelial cells The study indicates that the human ciliary and iridial epithelium contains a system of *zonulae occludentes* which represents a diffusion barrier to high molecular water soluble substances This is consistent with previous studies in several species of animals

Key words ciliary body – iris – epithelium peroxidase – permeability – microscopy electron – human

It has been demonstrated in several species of animals that when horseradish peroxidase (PO) is introduced into the bloodstream as a protein tracer it permeates the vessels and the stroma of the ciliary processes and the movement

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of the tracer towards the posterior chamber is blocked apically in the lateral intercellular spaces of the non pigmented epithelial cells (Shiose 1970 Smith 1971 Vegge 1971 Uusitalo Palkama & Stjernschantz 1973) These cells are girdled by a system of *zonulae occludentes* comprising an important structure of the blood aqueous barrier There is also evidence that the posterior epithelial cells of the rabbit iris are girdled by *zonulae occludentes* Thus the movement of PO *in vivo* as well as *in vitro* in the intercellular spaces of the iridial epithelium is blocked apically in the lateral intercellular spaces of the posterior epithelial cells in this species (Pedersen 1975 Pedersen & Tønjum 1975)

The purpose of the present study was to investigate the permeation of PO in the human iridial and ciliary epithelium in order to locate a possible diffusion barrier to high molecular substances in these epithelia

Material and Methods

Two human eyes were used One eye was enucleated from a female 42 years old and the other from a male 63 years old The eyes were enucleated because they had small malignant melanomata of the posterior pole By clinical examination of the eyes no pathological changes were detected in the anterior segments

Immediately after enucleation the anterior segments of the eyes were removed and placed in Krebs Ringer bicarbonate solution (pH 7 4) with glucose (5 mg/ml)

Sectors of the ciliary body and iris were mounted between two lucite chambers having apertures of 3 mm in diameter facing each other The specimens covered completely the aperture The stromal side of the ciliary body or the anterior surface of the iris faced one chamber while the epithelial side with the ciliary processes or posterior side of the iris faced the other The epithelial side chamber contained the buffered solution and the stromal side chamber contained the same solution with the addition of horseradish peroxidase (PO) (Sigma type II) at a concentration of 2 mg/ml

The solutions were stirred with teflon coated magnets rotating at 375 rev/min After 2 h at room temperature the specimens were fixed in 2 5 % glutaraldehyde in 0 1 M phosphate buffer (pH 7 4) for 2 h The specimens were then cut into thin slices of about 0 5 mm in thickness The tissue pieces were washed over night in 0 1 M phosphate buffer (pH 7 4) containing 5 % sucrose They were then incubated in tris HCl buffered diaminobenzidine H_2O_2 solution (pH 7 6) at room temperature for 30–60 min (Karnovsky 1967) The tissues were postfixed in 1 % OsO_4 in Millonig s phosphate buffer for 1 h dehydrated in ethanol treated with propylene oxide and embedded in Epon 812

Ultrathin sections were made with an LKB Ultratome The sections were contrasted with an aqueous solution of uranyl acetate and alkaline lead Electron micrographs were taken with a Siemens Elmiscope 1A

Results

Under the present experimental conditions peroxidase reaction products (PORP) were demonstrated throughout the stroma of the iris and of the ciliary processes In the ciliary epithelium the tracer was found throughout the lateral intercellular spaces of the pigmented epithelium as well as in the intercellular spaces between the pigmented and the non pigmented epithelial cells Only the most apical sections of the lateral intercellular spaces of the non pigmented

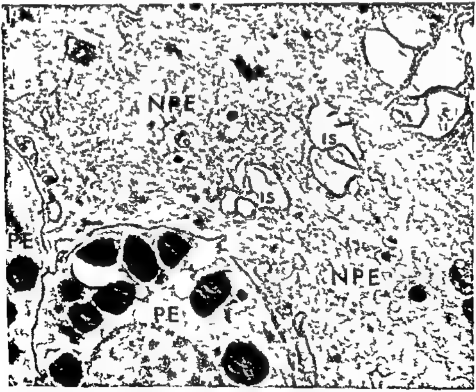

Fig 1

Ciliary epithelium The lateral intercellular space between the pigmented epithelial cells (PE) as well as the intercellular space between the pigmented and the non pigmented epithelial cells (NPE) contains peroxidase reaction product while this is not present in the lateral intercellular space (is) of the non pigmented epithelium × 10 000

of the tracer towards the posterior chamber is blocked apically in the lateral intercellular spaces of the non pigmented epithelial cells (Shiose 1970, Smith 1971, Vegge 1971, Uusitalo, Palkama & Stjernschantz 1973). These cells are girdled by a system of *zonulae occludentes* comprising an important structure of the blood aqueous barrier. There is also evidence that the posterior epithelial cells of the rabbit iris are girdled by *zonulae occludentes*. Thus the movement of PO *in vivo* as well as *in vitro* in the intercellular spaces of the iridial epithelium is blocked apically in the lateral intercellular spaces of the posterior epithelial cells in this species (Pedersen 1975, Pedersen & Tonjum 1975).

The purpose of the present study was to investigate the permeation of PO in the human iridial and ciliary epithelium in order to locate a possible diffusion barrier to high molecular substances in these epithelia.

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The solutions were stirred with teflon coated magnets rotating at 375 rev/min. After 2 h at room temperature the specimens were fixed in 2.5 % glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for 2 h. The specimens were then cut into thin slices of about 0.5 mm in thickness. The tissue pieces were washed over night in 0.1 M phosphate buffer (pH 7.4) containing 5 % sucrose. They were then incubated in tris-HCl buffered diaminobenzidine-H_2O_2 solution (pH 7.6) at room temperature for 30–60 min (Karnovsky 1967). The tissues were postfixed in 1 % OsO_4 in Millonig's phosphate buffer for 1 h, dehydrated in ethanol, treated with propylene oxide and embedded in Epon 812.

Ultrathin sections were made with an LKB Ultratome The sections were contrasted with an aqueous solution of uranyl acetate and alkaline lead Electron micrographs were taken with a Siemens Elmiscope 1A

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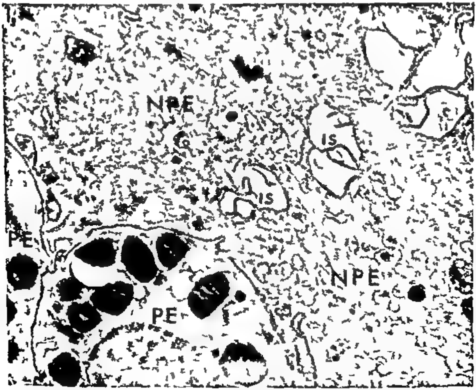

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The purpose of the present study was to investigate the permeation of PO in the human iridial and ciliary epithelium in order to locate a possible diffusion barrier to high molecular substances in these epithelia

Material and Methods

Two human eyes were used One eye was enucleated from a female 49 years old and the other from a male 63 years old The eyes were enucleated because they had small malignant melanomata of the posterior pole By clinical examination of the eyes no pathological changes were detected in the anterior segments

Immediately after enucleation the anterior segments of the eyes were removed and placed in Krebs Ringer bicarbonate solution (pH 7 4) with glucose (5 mg/ml)

Sectors of the ciliary body and iris were mounted between two lucite chambers having apertures of 3 mm in diameter facing each other The specimens covered completely the aperture The stromal side of the ciliary body or the anterior surface of the iris faced one chamber while the epithelial side with the ciliary processes or posterior side of the iris faced the other The epithelial side chamber contained the buffered solution and the stromal side chamber contained the same solution with the addition of horseradish peroxidase (PO) (Sigma type II) at a concentration of 2 mg/ml

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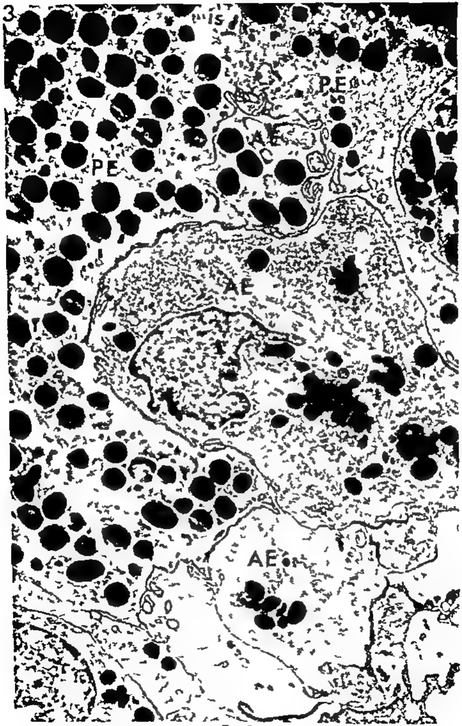

Fig 3

epithelial cells contained PORP whereas the rest of these intercellular spaces did not contain any tracer (Fig 1) The staining of these intercellular spaces discontinued abruptly at points where the intercellular spaces apparently were occluded (Fig 2) These points were interpreted as representing *zonulae occludentes (z o)*

Close to the z o at the basal side *zonulae adhaerentes* were regularly present and further down in the basal direction one or more desmosomes were found (Fig 2) This appeared to be a typical distribution pattern of intercellular junctional complexes in the non pigmented ciliary epithelium

In the epithelium of the iris the distribution pattern of PORP was essentially the same as in the ciliary epithelium Thus the tracer was found throughout the lateral intercellular spaces of the anterior epithelium and between the anterior and posterior epithelial cell layer (Fig 3) The permeation of the tracer was blocked apically between the posterior epithelial cells and only the most

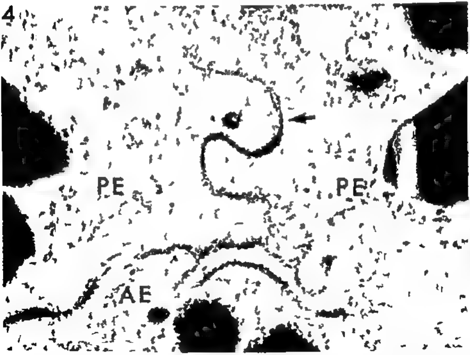

Fig 4

Detail from the iridial epithelium Peroxidase reaction product is present in the intercellular space between anterior (AE) and posterior (PE) epithelial cells A section of the apical part of the lateral intercellular space between the posterior epithelial cells also contains reaction product The tracer is not present in this intercellular space at the basal side of a narrowing (arrow) of the intercellular space × 48 000

apical sections of these intercellular spaces contained PORP (Fig 4) The permeation of the tracer had come to a stop at points where the intercellular spaces were narrowed in the same manner as in the ciliary epithelium

Comments

In the present *in vitro* system the distribution pattern of PORP when the tracer was applied to the stromal side is the same in the human ciliary epithelium as previously demonstrated in the rabbit (Pedersen & Tønjum 1975) Furthermore the distribution of PORP is the same as in living animals when the tracer has been administered intravenously (Shiose 1970 Smith 1971 Vegge 1971)

The barrier site is supposed to be a system of *onulae occludentes* since these are the only known junctional complexes that effectively block the permeation of PORP through intercellular spaces This is also in accordance with the observations of Reale & Spitznas (1975) who have demonstrated the presence of *onulae occludentes* in the human non pigmented ciliary epithelium by freeze etching

The distribution pattern of PORP in the iridial epithelium is the same as in the ciliary epithelium indicating that also the posterior epithelial cells of the iris are girdled by *onulae occludentes* Previously the same observation has been made in the rabbit iridial epithelium by the same *in vitro* technique as here (Pedersen & Tonjum 1975) This was also found *in vivo* when the barrier of the iris vessels was broken down by prostaglandins leading to a soaking of the iris stroma by PO (Pedersen 1975)

The succession of the different junctional complexes between the non pigmented ciliary epithelial cells is the same as in many other epithelia (Farquhar & Palade 1963) This has also previously been documented in the monkey ciliary epithelium (Vegge 1972)

In the animals the blood aqueous barrier to PO may be studied *in vivo* as well as *in vitro* In the human eye however one has to rely upon *in vitro* studies of tissues from newly enucleated eyes The present study has shown that the location and the type of the barrier to high molecular watersoluble substances between the ciliary stroma and the posterior chamber is the same as in a variety of animal eyes Moreover we have found a barrier of the same type in the iridial epithelium which represents a diffusion barrier between the posterior and the anterior chamber and which in turn may explain the phenomenon of iris bombe in seclusio pupillae

References

Farquhar M G & Palade G E (1963) Junctional complexes in various epithelia J Cell Biol 17 375–412

Karnovsky M J (1967) The ultrastructural basis of capillary permeability studied with peroxidase as a tracer J Cell Biol 35 213–236

Pedersen O O (1975) Electron microscopic studies on the blood aqueous barrier of prostaglandin treated rabbit eyes II Iris Acta ophthal (Kbh) 53 690–709

Pedersen O O & Tonjum A M (1975) *In vitro* studies on peroxidase movement in the epithelium of prostaglandin treated rabbit ciliary bodies Acta ophthal (Kbh) 53 673–684

Reale E & Spitznas M (1975) Freeze fracture analysis of junctional complexes in human ciliary epithelia Albrecht v Graefes Arch Ophthal 195 1–16

Shiose Y (1970) Electron microscopic studies on blood retinal and blood aqueous barriers Jap J Ophthal 14 73–87

Smith R S (1971) Ultrastructural studies of the blood aqueous barrier I Transport of an electron dense tracer in the iris and ciliary body of the mouse Amer J Ophthal 71 1066–1077

Uusitalo R Palkama A & Stjernschantz J (1973) An electron microscopical study of the blood aqueous barrier in the ciliary body and iris of the rabbit Exp Eye Res 17 49–63

Vegge T (1971) An epithelial blood aqueous barrier to horseradish peroxidase in the ciliary processes of the vervet monkey (*Cercopithecus aethiops*) Z Zellforsch 114 309–320

Vegge T (1972) A blood aqueous barrier to small molecules in the ciliary processes of the vervet monkey (*Cercopithecus aethiops*) Z Zellforsch 135 483–499

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RELATIVE CONTENTS OF SODIUM POTASSIUM WATER AND DRY MATTER IN HUMAN SENILE CATARACTOUS LENSES IN RELATION TO ANTERIOR CAPSULAR/SUBCAPSULAR OPACITY

BY

A KLAUBER and A BRUUN LAURSEN

In 49 human senile cataractous lenses the sodium and potassium concentrations of the lens water as well as the water and dry weight percentages were examined It was found justifiable to classify the lenses into three categories on the basis of correlated biomicroscopic and biochemical findings

1 Immature cataractous lenses *without anterior capsular/subcapsular opacity (ac sco)* were characterized by low CNa_L^+ high CK_L^+ and low sums of $CNa_L^+ + CK_L^+$

2 Immature cataractous lenses with *ac sco* were characterized by intermediate values of CNa_L^+ and CK_L^+ as well as high sums of $CNa_L^+ + CK_L^+$

3 Totally opaque lenses (these lenses had 80–100 % of ac sco) were characterized by high CNa_L^+ low CK_L^+ high sums of $CNa_L^+ + CK_L^+$ high water and low dry weight percentages

It was found that in immature cataractous lenses increasing extension of ac sco was correlated to *increasing* CNa_L^+ *and increasing ratios of* CNa_L^+/CNa_A^+ as well as to decreasing CK_L^+ and decreasing ratios of

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CNa_L^+ and CK_L^+ = sodium and potassium concentrations respectively in meq/kg lens water CNa_A^+ and CK_A^+ = sodium and potassium concentrations respectively in meq/kg aqueous humour

CK_L^+/CK_S^+ The sums of $CNa_L^+ + CK_S^+$ increased There was a correlation of the extent of ac sco to the water and dry weight percentages of the immature senile cataractous lenses with ac sco viz a negative correlation for water and a positive one for the dry weight However these latter two correlations may be due to chance significances the level of significance being only $0.05 > P > 0.02$ in both instances
Lenses which were estimated to have $\geq 30\%$ of ac sco were found to be more opaque than lenses with $\leq 25\%$ of ac sco

Key words cataract senile – cataract opacity anterior capsular/subcapsular – sodium – potassium – water – dry weight

Kinsey & Reddy (1965) found evidence that active cation transport of the lens takes place in the epithelium which in clear lenses forms a single layer of cells beneath the anterior capsule of the lens Therefore the biomicroscopical appearance of the anterior surface of the lens might be an important indicator of the cation balance of the lens The concentration of sodium in the lens is considered to be a sensitive index of its metabolic integrity (Trayhurn & van Heyningen 1971)

Bruun Laursen (1976) proposed a classification of human senile cataracts into three categories (see Methods) on the basis of correlation between the biomicroscopical appearance of the anterior surface of the lens and the lens ribonucleotide concentrations In the following it will be shown that this classification is also justifiable as far as the concentrations of sodium and potassium in the lens water and to some extent the lens water and dry weight percentages are concerned The dry weight of the lens is considered to be practically identical with its protein fraction (Kuck 1975)

Material

The material of the present study includes 49 senile cataractous lenses removed from 62 95 year old patients during cataract operations in retrobulbar anaesthesia (1 5–2 0 ml of 1 % mepivacaini chloridum NFN without adrenaline or noradrenaline) Peroperative mydriasis was produced by means of 0 5 % cyclopentolate In 20 cases aqueous humour for sodium and potassium determinations was aspirated immediately before the anterior chamber was opened (corneoscleral incision)

The patients were fasted for about 10 h before operations The following groups of patients were excluded Patients with diabetes mellitus or a fasting blood sugar concentration above 6 1 mm 1 1 patients treated with drugs of the digitalis group or cortico-

steroids during the period of cataract development patients with additional eye disease and patients treated with diuretics We also excluded lenses treated with the proteolytic enzyme α chymotrypsin during the operation and lenses extracted extracapsularly

Methods

On the basis of preoperative slit lamp examinations in mydriasis (cyclopentolate 0 5 % + phenylephrine 10 %) the lenses were classified into three catagories (Bruun Laursen 1976) 1 immature cataractous lenses without anterior capsular/subcapsular opacity (ac sco) 2 immature cataractous lenses with ac sco 3 totally opaque lenses (which had from 80 % to 100 % of ac sco) The extent of visible ac sco was estimated in relation to the visible part of the anterior surface of the lens and expressed as a percentage We were unable to find a better way to express the extent of ac sco All the lenses were evaluated by the same person Moreover by means of slit lamp and ophthalmoscopic examinations the immature cataractous lenses were graded according to the density and extension of the opacities grade 1 lenses comprised cataracts of slight extension and a high degree of transparency while grade 2 lenses were more severely affected

The lenses were cryo extracted catiously wiped with fine gauze and dropped into liquid nitrogen The lenses were stored at −20°C one week at the most until they were pulverized as described by Bruun Laursen (1976) The frozen lens powder was mixed and transferred to a 5 ml Potter Elvehjem homogenizer containing 1 25 g of 10 % w/v of trichloroacetic acid (van Heyningen 1972) Homogenization followed at 100 r p m for two min About 85 % of the homogenate was poured into a 12 ml Pyrex tube and centrifuged at 3000 r p m for 10 min The sodium and potassium concentrations of the supernatant were determined by means of an FLM 3 flame photometer (Radiometer) The precipitate was dried in a kiln at 108°C until constant weight was obtained usually after 48 h

The weights in mg of lens powder trichloroacetic acid homogenate and dry weight of the lens powder were recorded The supernatant was calculated by subtraction of the dry weight from the wet weight of the lens powder

For preliminary determinations of Na^+ and K^+ samples of 25 μl of supernatant were added to 4 97 ml of a 3 0 mM lithium sulphate solution which was used as an internal standard If values below 50 meq/l or above 150 meq/l were read new dilutions were prepared (up to 400 μl supernatant were added to 4 6 ml of lithium sulphate (3 19 mM) because the sensitivity of the flame photometer is maximal in the interval of 50–150 meq of Na^+ and K^+/l Standard solutions of 50 75 100 and 150 meq of Na^+ and K^+/l were used in 3 0 mM lithium sulphate for daily control of the apparatus

Recovery experiments were performed with cataractous lenses the median recovery for Na^+ was 105 % and for K^+ the median recovery was 103 % The median difference between the dry weight percentages was 1 % (N = 10)

The concentrations of Na^+ and K^+ in the lens water as well as the dry weight percentages were determined in the lenses from both eyes of 11 pigs The median differences were 3 5 meq /kg lens water for sodium (median $C_{Na_L^+}$ = 19 9) 4 1 meq /kg lens water for potassium (median $C_{K_L^+}$ = 125 3) The median difference between the

dry weight percentages was 0 3 % (median dry weight percentage = 30 0 %) The concentrations of sodium and potassium were expressed in meq./kg lens water and meq./kg aqueous humour the lens dry weight and water contents were expressed in mg

The Wilcoxon test for two samples (the Mann Whitney test) was used for comparisons between individual groups Spearman's rank correlation analysis was used to test correlations between the parameters in question and the extent of ac sco The range represents the difference between the highest and the lowest observations

Table 1

Concentrations (meq./kg lens water) and ratios for sodium and potassium as well as wet and dry weight percentages in human senile cataractous lenses Group 1 *immature cataractous lenses without anterior capsular subcapsular opacity (ac sco) Group 2* immature cataractous lenses *with ac sco* Group 3 totally opaque lenses (they had 80–100 % of ac sco)

Parameter	Group	Median	Percentiles		Range	N
			25 %	75 %		
$C_{Na_L^+}$	1	36	27	41	24	13
	2	111	45	1 1	198	24
	3	196	185	207	49	17
$C_{K_L^+}$	1	164	159	170	41	13
	2	99	61	158	156	24
	3	24	19	27	18	17
$C_{Na_L^+} + C_{K_L^+}$	1	195	191	209	50	13
	2	214	204	228	95	24
	3	224	209	232	52	17
H_2O %	1	67	66	68	6	13
	2	65	61	68	16	24
	3	74	68	78	14	17
Dry weight %	1	33	32	34	6	13
	2	35	37	39	16	24
	3	27	22	32	14	17
$\frac{C_{Na^+}\ \text{lens water}}{C_{Na}\ \text{aqueous}}$	1	0 96			0 1	4
	2	1 01	0 33	1 20	1 11	11
	3	1 32			0 11	5
$\frac{C_K\ \text{lens water}}{C_K\ \text{aqueous}}$	1	46			16	4
		20	16	40	41	11
	3	5			3	5

Results

Table I gives medians percentiles and ranges for the three cataract groups in question For the concentrations of sodium in the lens water ($^{C}Na_L^+$) an increasing tendency was found from immature cataractous lenses without anterior capsular/subcapsular opacity (ac sco) via immature cataractous lenses with ac sco and a maximum was reached in the group of totally opaque lenses (which had 80–100 % of ac sco) For the concentration of potassium in lens water ($^{C}K_L^+$) a falling gradient was found through these three groups

The group of immature cataractous lenses *without ac sco* had lower $^{C}Na_L^+$ ($P < 0.01$) and lower ratios of $^{C}Na_L^+/^{C}Na_A^+$ ($0.05 > P > 0.02$) as well as higher $^{C}K_L^+$ – $P < 0.01$ – and higher ratios of $^{C}K_L^+/^{C}K_A^+$ ($0.05 > P > 0.02$) than had immature cataractous lenses with ac sco Furthermore immature cataractous lenses *without ac sco* had lower sums of $^{C}Na_L^+ + ^{C}K_L^+$ ($P < 0.01$) slightly higher lens water and slightly lower dry weight percentages than had

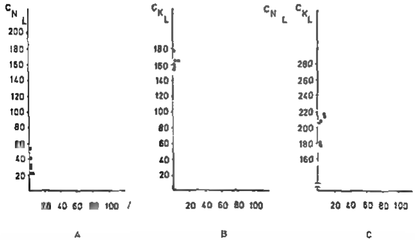

Fig 1

Correlations between the concentrations of sodium potassium, and the sums of sodium and potassium ion concentrations in meq./kg lens water on the one hand and the extent of anterior capsular/subcapsular opacity (abscissas) in 24 immature cataractous lenses with anterior capsular/subcapsular opacity By means of Spearman s rank correlation analysis the following rank correlation coefficients (R_s) and significance levels were found

A R – 0.8[illegible]6[illegible] $P < 0.001$
B R = –0.8071 $P < 0.001$
C R – 0.63[illegible] $0.01 > P > 0.001$

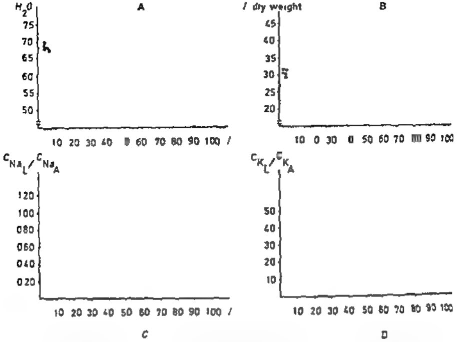

Fig 2

Correlations between lens water and dry weight percentages as well as the concentration ratios of sodium in lens water/sodium in the aqueous (CNa_L^+/CNa_A^+) and potassium in lens water/potassium in the aqueous (CK_L^+/CK_A^+) on the one hand and the extent of anterior capsular subcapsular opacity (ac sco) – abscissas – on the other hand in immature senile cataractous lenses with ac sco The water percentages of the lenses were calculated by subtraction of the dry weights from the wet weights By means of Spearman's rank correlation analysis the following rank correlation coefficients (R_s) and significance levels were found

A	$R = -0.4180$	$0.05 > P > 0.02$	$N = 24$
B	$R = 0.4472$	$0.05 > P > 0.02$	$N = 24$
C	$R_s = 0.7273$	$0.02 > P > 0.01$	$N = 11$
D	$R_s = -0.7705$	$0.02 > P > 0.01$	$N = 11$

immature cataractous lenses with ac sco ($0.05 > P > 0.2$ in both instances – chance significances?) See Table I

Immature cataractous lenses *with ac sco* had lower CNa_L^+ ($P < 0.01$) lower ratios of CNa_L^+/CNa_A^+ ($P < 0.01$) higher CK_L^+ and higher ratios of CK_L^+/CK_A^+ ($P < 0.01$ in both instances) than had totally opaque lenses No significant difference was found between the sums of $CNa_L^+ + CK_L^+$ of the two groups. Furthermore lower water and higher dry weight percentages were found in immature cataractous lenses with ac sco than in totally opaque lenses ($P < 0.01$ in both instances) See Table I

The ranges are large for $^CNa_L^+$ $^CK_L^+$ $^CNa_L^+ + {}^CK_L^+$ $^CNa_L^+/^CNa_A^+$ and for $^CK_L^+/^CK_A^+$ in the group of immature cataractous lenses with ac sco (see Table I) The reason for this appears in Figs 1 and 2 where the correlations are described graphically between the parameters in question and the extent of ac sco in the 24 immature senile cataractous lenses *with ac-sco* The following changes were seen as the extension of ac sco increased increasing $^CNa_L^+$ (Fig 1 A) decreasing $^CK_L^+$ (Fig 1 B) increasing sums of $^CNa_L^+ + {}^CK_L^+$ (Fig 1 C) slightly decreasing water and slightly increasing dry weight per centages (Figs 2 A and 2 B) – $0\,05 > P > 0\,02$ chance significances? – increasing ratios of $^CNa_L^+/^CNa_A^+$ (Fig 2 C) and decreasing ratios of $^CK_L^+/^CK_A^+$ (Fig 2 D)

In the group of immature cataractous lenses *without ac-sco* all 18 lenses but one were grade 1 (see Methods) and in the group of immature cataractous lenses *with ac-sco* 13 lenses were grade 1 and 11 lenses were grade 2 In this selected material (see Methods) all grade 1 lenses *with ac sco* had $\leq 25\,\%$ of ac sco while 10 out of 11 grade 2 lenses *with ac sco* had $\geq 30\,\%$ of ac sco However grade 1 lenses with 100 % of ac sco have been seen in a few eyes not included in this material No age concentration correlations were found for $^CNa_L^+$ and $^CK_L^+$ in the age interval of 62–87 years (group II – Table I)

The following observations point to the essential role played by ac sco in the cation balance in early cataract as compared with other types of lens opacity eight grade 1 immature cataractous lenses *with 10–25 % of ac sco* (and deep cortical nuclear and posterior subcapsular opacities) had higher ($P < 0\,01$) median $^CNa_L^+$ (97 meq./kg range = 113) than had six grade 1 immature cataractous lenses with posterior subcap sular (and deep cortical and nuclear) cataract and without ac sco (median $^CNa_L^+$ = 40 meq./kg range = 19) The median $^CK_L^+$ was lower ($0\,05 > P > 0\,02$) in the eight lenses *with ac sco* (median $^CK_L^+$ = 116 meq./kg range = 99) than in the six lenses with posterior subcapsular cataract and without ac sco (median $^CK_L^+$ = 161 meq./kg range = 20) One lens with a pure 100 % posterior subcapsular opacity and without ac sco had a $^CNa_L^+$ of 19 meq./kg and a $^CK_L^+$ of 178 meq./kg However this lens was excluded from our material because of a slightly pathological oral glucose tolerance test When the same eight lenses *with ac sco* were compared with 11 grade 1 immature cataractous lenses with deep cortical (and posterior subcapsular and nuclear) opacity and without ac sco higher ($P < 0\,01$) $^CNa_L^+$ was found in the lenses with *ac sco* than in the lenses without ac sco (median $^CNa_L^+$ = 36 meq./kg range = 24) The $^CK_L^+$ was lower ($P < 0\,01$) in the lenses *with ac sco* than in the lenses without ac sco (median $^CK_L^+$ = 162 meq./kg range = 96)

The $^CNa_A^+$ and $^CK_A^+$ did not differ significantly between the three groups in question The median concentrations for 20 samples were $^CNa_A^+$ = 147 meq./kg range = 10 $^CK_A^+$ = 3 7 meq./kg range = 1 0 Nor did the ratios of $^CNa_A^+$ or $^CK_A^+/^CNa^+$ or $^CK^+$ in plasma water differ significantly from group to group

The median Na^+ ratio was 0.92, range = 0.07, and the median K^+ ratio was 0.80, range = 0.18. The water content of plasma was taken as 91 %.

The median age (69 years) of 24 patients with immature cataracts with ac. sco. was lower ($P < 0.01$) than that of patients with immature cataracts without ac. sco. (77 years). The median age for patients with totally opaque lenses was 76 years.

Discussion

This study points to a correlation between the extent of anterior capsular/subcapsular opacity and the concentrations of Na^+ and K^+ in the water phase of human senile cataractous lenses. This observation does not appear to have been reported before in the literature.

The precise site(s) and nature of the histopathology in the diffuse type of ac. sco. in human senile cataract are unknown. On histopathological examinations de Wecker (1886) found vacuolation and degeneration of epithelial cells in certain cases of senile cataract. Font & Brownstein (1974) found that both epithelium and lens capsule were involved in a study on the histopathology of anterior polar subcapsular cataract. Brown & Tripathi (1973) found evidence in electron microscopic studies that the anterior lens fibres and to some extent the lens epithelium were involved when the anterior subcapsular clear zone of the lens was lost on biomicroscopic examination. The changes occurring in the epithelium were vesiculation probably related to cystic mitochondria, variation in cytoplasmic density and widening of extracellular spaces. Loss of the anterior clear zone was considered to be associated with progressive cataract. Yanoff (1975) described the development of anterior subcapsular cataract: after a noxious influence on the anterior lens surface (e.g. iritis) or after a trauma some epithelial cells become necrotic. Their place is taken by migrating adjacent epithelial cells which proliferate, form a subcapsular plaque and undergo metaplasia so as to become fibroblasts. These fibroplasts lay down a connective tissue scar, which is encapsulated between a duplicated lens capsule, the anterior surface of which is wrinkled. A slit lamp photograph showed ac. sco. to be located in and/or just beneath the anterior capsule of the lens, i.e. close to the epithelium (Bruun Laursen 1976).

The low lens water concentrations of Na^+ and the high lens water concentrations of K^+ that occur in clear lenses (e.g. Maraini & Mangili 1973) are dependent on carrier mechanism(s) which actively transports Na^+ out of and K^+ into the lens. This carrier system(s) is chiefly located in the lens epithelium (Kinsey & Reddy 1965). Bonting (1965) concluded that the Na-K-ATPase

which he found exclusively in the epithelium of cat calf and rabbit lenses is identical with or very closely related to the ATP requiring cation transport system of the lens In rat lenses Na K ATP ase is located on the surfaces of the epithelial cells (Palva & Palkama 1974) The findings in the present study that changes in ${}^{C}Na_L^+$ and ${}^{C}K_L^+$ are correlated to an increasing extension of ac sco whereas the water percentage does not increase in this situation show that ac sco is associated with a relative defect in the Na^+ K^+ pump system or/and changes in the permeability for Na^+ and for K^+ of the lens membrane

Water is often assumed to follow Na^+ by passive diffusion In the present study water percentages were no higher in the group of immature cataractous lenses with ac sco than in immature cataractous lenses without ac sco but ${}^{C}Na_L^+$ and the sums of ${}^{C}Na_L^+ + {}^{C}K_L^+$ were higher in lenses with ac sco High ${}^{C}Na_L^+$ not accompanied by high water percentages were also reported by van Heyningen (1972) and by Maraini & Mangili (1973) Duncan (1973) suggested that negatively charged macromolecules within the lens might be responsible for the fact that ${}^{C}Na_L^+$ often exceeds the ${}^{C}Na_a^+$ when the sodium pump on the lens membranes fails to extrude Na^+ from the lens The wet weights of totally opaque lenses are lower than those of clear lenses (Maraini & Mangili 1973) Therefore the high water and low dry weight percentages of the totally opaque lenses may be due to a leak of proteins of low molecular weight from the lenses to the aqueous humour as suggested by Mach (1963) Charlton & van Heyningen (1968) and van Heyningen (1972) rather than to a gain in water

It has been claimed by Maraini & Mangili (1973) that the balance of ${}^{C}Na_L^+$ and ${}^{C}K_L^+$ in senile cataractous lenses was upset in cortical but not in nuclear opacities Pau (1974) claimed that this balance was upset in posterior subcapsular but not in supranuclear cortical cataract The present study shows that increasing extension of ac sco in the area where the cation pump(s) is assumed to be located is closely correlated to increasing ${}^{C}Na_L^+$ and to decreasing ${}^{C}K_L^+$ and that in early cataract ac sco seems to be more critical than other types of opacity as far as ${}^{C}Na_L^+$ and ${}^{C}K_L^+$ are concerned We cannot decide whether ac sco is the cause of the changes in the cation balance or whether underlying mechanisms cause changes in the cation balance and subsequent changes in the biomicroscopic appearance of the anterior lens surface in senile cataract

It appears justifiable to maintain the biomicroscopical classification of senile cataractous lenses used in Table I

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References

Bonting S L (1965) Na K activated adenosinetriphosphatase and active cation transport in the lens *Invest Ophthal 4* 723–737

Brown N & Tripathi R (1974) The loss of the anterior subcapsular clear zone of the lens Prognostic significance in cataract formation *Trans ophthal Soc U K 94* 29–45

Bruun Laursen A (1976) Concentrations of some ribonucleotides L lactate and pyru vate in human senile cataractous lenses with special reference to anterior capsular subcapsular opacity *Acta ophthal (Kbh) 54* 677–692

Charlton J M & van Heyningen R (1968) An investigation into the loss of proteins of low molecular size from the lens in senile cataract *Exp Eye Res 7* 47–55

Duncan G (1973) Role of membranes in controlling ion and water movements in the lens In Ciba Foundation Symposium 19 (new series) Ed *The human lens – in relation to cataract* pp 99–116 Associated Scientific Publishers Amsterdam London New York

Font R L & Brownstein S (1974) A light and electron microscopic study of anterior subcapsular cataracts *Amer J Ophthal 78* 972–984

van Heyningen R (1972) The human lens I A comparison of cataracts extracted in Oxford (England) and Shikarpur (W Pakistan) *Exp Eye Res 13* 136–147

Kinsey V E & Reddy D V N (1965) Studies on the crystalline lens XI The relative role of the epithelium and capsule in transport *Invest Ophthal 4* 104–116

Kuck J F R Jr (1975) Composition of the lens In Bellows J G Ed *Cataract and abnormalities of the lens* pp 69–96 Grune & Stratton Inc New York San Francisco London

Mach H (1963) Untersuchungen von Linseneiweiss und Mikroelektrophorese von wasser loslichem Eiweiss im Altersstar *Klin Mbl Augenheilk 143* 689–710

Maraini G & Mangili R (1973) Differences in proteins and in the water balance of the lens in nuclear and cortical types of senile cataract. In Ciba Foundation Sym posium 19 (new series) Ed *The human lens – in relation to cataract* pp 79 97 Asso ciated Scientific Publishers Amsterdam London New York

Palva M & Palkama A (1974) Sodium potassium activated adenosine triphosphatase (Na K ATP ase) activity in the rat lens A histochemical and biochemical study *Acta ophthal (Kbh) Suppl 123* 59–8

Pau H (1974) The pathogenesis of subcapsular opacities of the lens (permeability cataract) *Docum ophthal 37* 47–57

Trayhurn P & van Heyningen R (1971) Aerobic metabolism in the bovine lens *Exp Eye Res 12* 315–327

de Wecker L (1886) Cataracte capsulaire capsulo lenticulaire In Iwanoff A , Schwalbe G and Waldeyer W Eds *Traite complet d ophthalmologie Anatomie microscopique* Tome 12 pp 869–875 Delahaye A & Lecrosnier E Paris

Yanoff M (1975) Pathology of cataract In Bellows J G Ed *Cataract and abnormalities of the lens* pp 155–189 Grune & Stratton Inc New York San Francisco London

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PLACOID PIGMENT EPITHELIOPATHY PRESENTING AS AN ANTERIOR UVEITIS

A Case Report

BY

MARTIN LOWES

A young woman with acute posterior multifocal placoid epitheliopathy originally presented with signs and symptoms of an anterior uveitis Prior to the eye condition the patient had experienced headaches and malaise with some muscle and joint tenderness and had been treated with penicillin because of a dental infection The clinical and fluorescein angiographic findings are presented The evidence supports the concept of a primary vascular disturbance of the choriocapillaris with secondary involvement of the retinal pigment epithelium

Key words acute posterior multifocal placoid pigment epitheliopathy – anterior uveitis – retinal pigment epithelium – choriocapillaris – fluorescein angiography

The term acute posterior multifocal placoid pigment epitheliopathy (APMPPE) was coined by Gass (1968) to describe the clinical and fluorescein angiographic findings in three young adult female patients who presented with rapid loss of central vision as a consequence of multifocal yellow white placoid lesions situated in the posterior pole at the level of the pigment epithelium and choroid The disease process was characterised by a rapid resolution of these lesions and significant improvement in visual function but with permanent and marked alterations in the retinal pigment epithelium

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The condition does not appear to be so uncommon and is to be distinguished from the usual choroiditis lesions The present paper is concerned with a case of APMPPE which conforms to the original description by Gass with the exception of the fact that the patient presented with signs and symptoms of involvement of the anterior uveal tract

Case Report

A 28 year old woman consulted her ophthalmologist with a one week history of blurring of vision and redness of both eyes The patient had for several weeks experienced headaches and malaise with some muscle and joint tenderness Penicillin treatment had been started just prior to the onset of the eye condition because of a dental infection

The visual acuity of the right eye was 0 8 and of the left eye 0 4 Slit lamp biomicroscopy showed definite evidence of an anterior uveitis with conjunctival and ciliary injection aqueous flare and several large mutton fat precipitates The patient was treated with local corticosteroids

One week later although the iritis had improved the visual acuity of both eyes had become reduced to 0 1 There was evidence of involvement of the posterior uveal tract with elevation and pigment mottling in the macular area of both eyes

Laboratory Investigations

The following investigations were performed and the results were all within normal limits haemoglobin white cell count erythrocyte sedimentation rate blood glucose serum electrolytes Wassermann reaction, gonococcal complement reaction toxoplasmosis complement fixation reaction and antistreptolysin titre Radiology of the chest and nasal sinuses were normal Radiology of the teeth revealed apical and marginal paradontitis

Treatment

Systemic corticosteroid treatment was started with oral prednisone 60 mg daily with an initial prednisone supplement of methylprednisone 1500 mg intravenously

Fluorescein angiography

Fluorescein angiography was performed three weeks after the onset of the symptoms In the arteriovenous phase geographical areas of non fluorescence were seen corresponding to the fundus lesions In the course of the venous phase the edges of the lesions gradually became hyperfluorescent and indistinct (Fig 1 a) This was followed by a progressive and irregular staining of the remainder of the lesions (Figs 1 b and c) There was prolonged staining at the site of the lesions in the late phases The optic discs and retinal vessels were normal

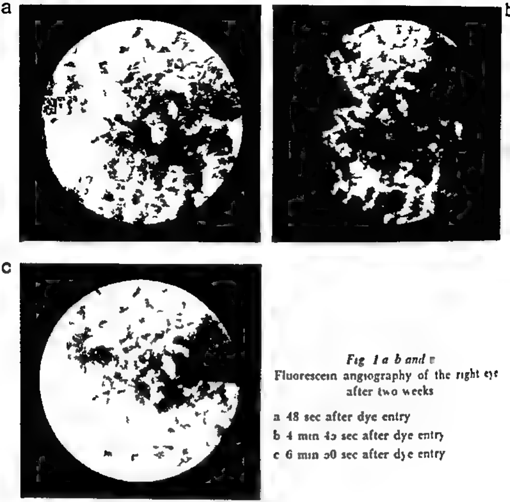

Fig. 1 a, b and c
Fluorescein angiography of the right eye after two weeks

a 48 sec after dye entry
b 4 min 45 sec after dye entry
c 6 min 50 sec after dye entry

Progress

At the time of fluorescein angiography the visual acuity of both eyes was 0.05. Ophthalmoscopy showed yellow white placoid lesions in the macular regions (Figs. 2 and 3). There were several similar but smaller lesions with slight pigment mottling situated on the nasal aspects of the optic discs.

One month later the visual acuity had improved to 0.4 in the right eye and 0.33 in the left eye. There was dense pigmentation of the placoid lesions but some lighter areas were still apparent within the lesions.

Result

The patient was examined fifteen months after the onset of the condition. The visual acuity of the right eye was 1.0 and of the left eye 0.4. The anterior chambers were normal. Ophthalmoscopy revealed 3–4 irregular charcoal black pigmented lesions on

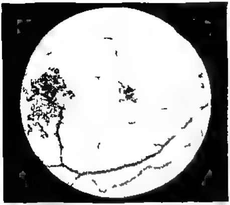

Fig 2
Right eye after two weeks

Fig 3
Left eye after two weeks

the nasal aspects of both optic discs with similar but larger areas in both posterior poles involving the fovea region on the left side (Figs 4 and 5) The visual fields were examined by means of a Bjerrum tangent screen There were no demonstrable scotomas on the right side but a small paracentral scotoma (9/2000 white object) was present on the left side

Corticosteroid treatment was continued for three months Improvement of the condition did not appear to be related to the steroid therapy as there was no improvement during the first two weeks of treatment Moreover visual acuity continued to improve after cessation of the treatment

Fig 4
Right eye after 15 months

Fig 5
Left eye after 15 months

Discussion

Gass (1968) felt that the term "pigment epitheliopathy should be used because clinically the pigment epithelium appeared to be the tissue most significantly affected Maumenee (1970) agreed with Gass and considered the disease to be one of several disease entities which could be distinguished from the non specific term uveitis Deutman et al (1973) felt that it was in the patients interest that even in the acute phase of this process when the visual acuity has greatly deteriorated they can be informed of the relatively favourable prognosis Gass and Deutman both questioned the value of steroid therapy Annesley et al (1973) in a series of 13 patients treated only four patients with oral corticosteroids the remaining nine patients received no treatment. No difference was noted in the final results Fitzpatrick & Robertson (1973) and Savino et al (1973) have also reported cases where no treatment was given.

In spite of the clinical fluorescein angiographic and electrophysiological studies performed on patients with this disease (Buskirk et al (1971) Ryan & Maumenee (1972) Deutman et al (1972) Kirkham et al (1972) Bird & Hamilton (1972) Fitzpatrick & Robertson (1973) Annesley et al (1973) Savino et al (1973) and Fishman et al (1974) there still remains speculation about the aetiology of the condition and the tissue which is primarily affected No cases have been studied histologically

When the clinical picture is examined more closely it can be seen that the disease neither behaves in the manner of a well documented pigment epithelial disease – such as fundus flavimaculatus or retinitis pigmentosa where visual deterioration is gradually progressive and non reversible nor in the manner of typical choroiditis where the final scarring is gross involving as it does retina, pigment epithelium and choroid with dense scotomas The great majority of eyes involved recover their full visual acuity without any residual scotomas in spite of gross pigment disturbance However in the case reported here there was pigment derangement in the foveal region of one eye with a residual deficit in visual acuity and a persistent scotoma

Fluorescein angiography is similar in all the cases that have been reported including the present one It is difficult to determine with certainty whether the fluorescein angiographic findings represent a choroidal vasculopathy (Buskirk et al 1971) or pigment epithelial damage (Gass 1968 Ryan & Maumenee 1972)

So far as anterior uveitis associated with APMPPE is concerned evidence of anterior chamber reaction has been described by Buskirk et al (1971) Deutman et al (1972) Ryan & Maumenee (1972) Fitzpatrick & Robertson (1973)

Annesley et al (1973) and Savino et al (1973) Altogether nine cases of APMPPE with anterior chamber involvement have been documented

The case described here is unusual in that it originally presented with signs and symptoms of an iritis Later the typical fundus picture of APMPPE developed The ophthalmoscopical changes with the very obvious dense black pigmentary lesions undoubtedly represent sequelae from involvement of the retinal pigment epithelium resembling as they do the pattern of hypertrophy of the retinal pigment epithelium as described by Purcell & Shields (1975)

The choriocapillaris retinal pigment epithelium and retinal receptors are intimately related and a disturbance in the choriocapillaris will have disastrous consequences on the function of both the retinal pigment epithelium and the retinal receptors The fact that in the present case there was initial involvement of anterior uveal tissue supports the concept that APMPPE is a primary choriocapillaritis with a secondary pigment epitheliopathy

There can be little doubt that the retinal pigment epithelium is the tissue most markedly affected and the term APMPPE would therefore appear to be suitable But whatever the primary site the fact remains that the condition is a clinical entity and can be distinguished from other uveitis types The prognosis is generally good regardless of whether treatment is given or not provided that the fovea is not involved in the stage of resolution

References

Annesley W H Tomer T L & Shields J A (1973) Multifocal placoid pigment epitheliopathy *Amer J Ophthal 76* 511–518

Bird A C & Hamilton A M (1972) Placoid pigment epitheliopathy presenting with bilateral serous retinal detachment *Brit J Ophthal 56* 881–886

Deutman A F Oosterhuis J A Boen Tan T N & Aan de Kerk A L (1972) Acute posterior multifocal placoid pigment epitheliopathy Pigment epitheliopathy or choriocapillaritis *Brit J Ophthal 56* 863–874

Deutman A F Boen Tan T N & Oosterhuis J A (1973) Acute posterior multifocal placoid pigment epitheliopathy *Ophthalmologica 167* 368–379

Fishman G A Rabb M F & Kaplan J (1974) Acute posterior multifocal placoid pigment epitheliopathy *Arch Ophthal (Chicago) 92* 173–177

Fitzpatrick P J & Robertson D M (1973) Acute posterior multifocal placoid pigment epitheliopathy *Arch Ophthal (Chicago) 89* 373–376

Gass J D M (1968) Acute posterior multifocal placoid pigment epitheliopathy *Arch Ophthal (Chicago) 80* 177–185

Kirkham T H ffytche T J & Sanders M D (1972) Placoid pigment epitheliopathy with retinal vasculitis and papillitis *Brit J Ophthal 56* 875–880

Maumenee A E (1970) Clinical entities in uveitis An approach to the study of intraocular inflammation *Amer J Ophthal 69* 1–2

Purcell J J & Shields J A (1975) Hypertrophy with hyperpigmentation of the retinal pigment epithelium *Arch Ophthal (Chicago) 93* 1122–1126
Ryan S J & Maumenee A E (1972) Acute posterior multifocal placoid pigment epitheliopathy *Amer J Ophthal 74* 1066–1074
Savino P J Weinberg R J Yassin J G & Pilkerton A R (1974) Diverse manifestations of acute posterior multifocal placoid pigment epitheliopathy *Amer J Ophthal 77* 659–662
Van Buskirk E M A Lessel S & Friedman E (1971) Pigmentary epitheliopathy and erythema nodosum *Arch Ophthal (Chicago) 85* 369–372

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NOTES ON THE DISTRIBUTION OF PSEUDO EXFOLIATION MATERIAL WITH PARTICULAR REFERENCE TO THE UVEOSCLERAL ROUTE OF AQUEOUS HUMOUR

BY

AMUND RINGVOLD and MARTIN DAVANGER

The distribution of pseudo exfoliation material along the uveoscleral route of aqueous humour has been studied by electron microscopy It turned out that such material is present only in the very first part of this exit pathway i e in the innermost zone of the connective tissue bordering the anterior chamber angle No pseudo exfoliation material was observed between the ciliary muscle cells in the suprachoroidal space or in the sclera It is concluded that transport of pseudo exfoliation material by flow of aqueous humour through the uveoscleral route to the bulbar and palpebral conjunctiva is improbable and accordingly the pseudo exfoliation material found in extrascleral tissue most likely arises in loco

Key words pseudo exfoliation syndrome – glaucoma – uveoscleral route

Pseudo exfoliation material (PE material) is present in 4–5 % of presumptive healthy people over 60 years of age (Tarkkanen 1962 Aasved 1969) About 2/3 of these persons develop capsular glaucoma because of reduced outflow facility probably due to PE material in the trabecular area (Dvorak Theobald 1954 *Horven 1966 Ringvold & Vegge 1971 Yamagishi 1976) In such eyes* similar material has also been found in many other regions both inside and outside the anterior bulbar segment (Busacca 1928 Gifford 1957 Ringvold 1973 Layden & Shaffer 1974 Speakman & Ghosh 1976 Sugar et al 1976) and so far its origin is a question of controversy Clinical observations (Barkan

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1936 Thomassen 1949 Tarkkanen 1962) strongly indicate that at least fragments of PE material are transported to the corneal endothelium and the trabecular region by aqueous humour On the other hand intraocular PE aggregates would have to pass through connective tissue and endothelial walls to arrive in bulbar and palpebral conjunctiva Since such infiltration of conjunctival tissue with PE material is hard to imagine in particular in its palpebral coating it has been suggested that this material is synthesized in different locations both inside and outside the bulbus (Ringvold 1972 1973)

In order to test whether and eventually to what extent PE material is transported by flow into connective tissue we have looked for this material along the uveoscleral route (Bill & Phillips 1971) of aqueous humour In addition some observations from the posterior part of the bulbus are included in this study

Material and Methods

Specimens from a total of seven persons (71–94 years old) were included in this study all of them showing PE material in the anterior segment of the eye by slit lamp examination Five of them were enucleated because of painful glaucoma whereas the last two underwent surgery for a malignant melanoma of the maxilla and the macula region of the retina respectively These two eyes were normotensive the first because of continuous pilocarpine during the last year and the second without any treatment Preoperative radiation treatment had not been applied in any case

After enucleation the bulbi were opened at equator level and five of them were fixed 1–2 h in 1 % OsO_4 adjusted to pH 7 3 with phosphate buffer Two of the glaucomatous eyes were fixed 2 h in 2 5 % glutaraldehyde buffered to pH 7 4 in 0 1 M phosphate and postfixed for 1 h in 1 % OsO_4 as above Tissue blocks were dehydrated in graded acetone or alcohol solutions and embedded in Araldite or Epon Sections were made with an LKB Ultrotome and stained with aqueous solutions of uranyl acetate and lead citrate Siemens Elmiskop IA and Philips FM 400 were used for this study

Results

Previous descriptions of the ultrastructure of PE material (Blackstad et al 1960 Bertelsen et al 1964 Ashton et al 1965) also apply to those made in this study and as in other regions single fibrils tended to form aggregates measuring several micron across PE material was found within the loose connective

Fig 1

Peripheral part of the anterior chamber (ac) limited by loose connective tissue (lct) Although not demonstrable with this magnification PE material was present in this tissue but not between ciliary muscle cells (cm) Large vessel filled with erythrocytes in the iris root (arrow) tm trabecular meshwork i iris stroma Toluidine blue staining ×220

tissue limiting the most peripheral part of the irido corneal angle illustrated in Fig 1 Corresponding to findings at the anterior iris surface (Ringvold 1970) the main part of this material was present within a 20 μ broad zone along the anterior chamber surface (Fig 2) In addition to this zone few aggregates of PE material appeared scattered in the connective tissue towards the ciliary muscle but it never occured between ciliary muscle cells nor in the transitional region between ciliary body and sclera PE material gradually decreased in the anglebordering connective tissue towards the scleral spur The PE material was either completely surrounded by normally appearing intercellular substance or in some instances was closely apposed to connective tissue cells (Fig 3) Intracellularly lying PE material was not observed

Fig. 2

Electron micrograph showing the region of loose connective tissue demonstrated in Fig. 1. Pseudo-exfoliation material (PE) is roughly confined to a 20–[illegible] μ broad zone of connective tissue bordering the anterior chamber (ac). cm: ciliary muscle; e: elastic material. ×2300

Fig 3

Electron micrograph showing details from the loose connective tissue indicated in Fig 1 Pseudo-exfoliation material (PE) closely apposed to connective tissue cells (ctc) Note marked indentations of the cell wall filled with PE material × 58 500

PE material was also searched for but not found in the retina (3 eyes) the optic nerve head and the anterior part of this nerve with adjacent connective tissue (2 eyes) the choroid (3 eyes) the ciliary muscle and the stroma of the ciliary processes (3 eyes) the sclera and the peripheral part of the cornea including the membrane of Descemet (2 eyes) and the anterior part of the superior rectus muscle (2 eyes)

Discussion

PE material has previously been observed in many different locations both inside and outside the anterior eye segment and this distribution may be due to a multiocular synthesis or the material may be transported into various regions by the way of aqueous humour One can easily imagine that fragments of PE material from the posterior chamber arrive at the corneal endothelium or between the inner trabecular sheets since this is the way of aqueous flow and the resistance for movements of greater particles over this distance is negligible It is however not obvious that such transport is responsible for the presence of PE material deep in the connective tissue (iris stroma conjunctiva) We know that latex spheres of 1 μ diameter are readily moved in the eye wall tissue appearing in the macular region of the uvea only 3 h after intracameral injection (Inomata Bill & Smelser 1972) In contrast to these round smooth particles PE fibrils are rather long ragged elements (up to 1 2 μ long and 370 Å across) and this shape makes it likely that higher resistance towards transport of such material will occur By mapping the distribution of PE material along the uveoscleral route which is a connective tissue exit pathway we may roughly estimate whether PE material is moved away in such tissue by aqueous humour flow This study shows that similar to the iris stroma (Ringvold 1970) great amounts of PE material are present within a [illegible]0 μ broad zone of connective tissue along the anterior chamber i e in the ciliary band whereas only few aggregates were found scattered deeper in the same tissue towards the ciliary muscle No PE material was found within the ciliary muscle the suprachoroid and the sclera i e along most of the uveoscleral route This observation indicates that PE material does not leave the intraocular compartment through this route otherwise one would expect to find a track of material from the chamber angle to episclera and conjunctiva Accordingly as previously stated (Ringvold 1973) it seems very unlikely that PE material outside sclera derives from an intraocular source and this conclusion is also supported recently by Speakman & Ghosh (1976) who demonstrated PE material in the conjunctiva of patients with intraocular PE material only in the fellow eye

According to Bill & Walinder (1966) the uveoscleral route is closed when using pilocarpine and in six of our cases this drug had been used for a long time However this study also includes one eye with PE syndrome enucleated because of malignant melanoma and this normotensive eye had not been treated with pilocarpine The fact that this eye showed the same distribution of PE material along the unconventional route as the other specimens supports the view that pilocarpine treatment is not responsible for the lack of PE material along most of this pathway

References

Aasved H (1963) The geographical distribution of fibrillopathia epitheliocapsularis so called senil exfoliation or pseudoexfoliation of the anterior lens capsule. *Acta ophthal (Kbh) 4* 192–810

Ashton N Shakib M., Collyer R & Blach R (1965) Electron microscopic study of pseudo exfoliation of the lens capsule *Invest Ophthal 4* 141–153

Barkan O (1936) A new operation for chronic glaucoma *Amer J Ophthal 19* 951–966

Bertelsen T I Drablos P A & Flood P R (1964) The socalled senile exfoliation (pseudoexfoliation) of the anterior lens capsule a product of the lens epithelium Fibrillopathia epitheliocapsularis *Acta ophthal (Kbh) 4?* 1096–1113

Bill A & Phillips C I (1971) Uveoscleral drainage of aqueous humour in human eyes *Exp Eye Res 12* 275–281

Bill A & Wålinder P E (1966) The effects of pilocarpine on the dynamics of aqueous humour in a primate (*Macaca irus*) *Invest Ophthal 5* 170–175

Blackstad T W Sunde O A & Trætteberg J (1960) On the ultrastructure of the deposits of Busacca in eyes with glaucoma simplex and so called senile exfoliation of the anterior lens capsule *Acta ophthal 38* 587–598

Busacca A (1928) Struktur und Bedeutung der Hautchenniederschlage in der vorderen und hinteren Augenkammer *Arch Ophthal (Chicago) 119* 135–176

Dvorak Theobald G (1954) Pseudo exfoliation of the lens capsule *Amer J Ophthal 37* 1–1?

Gifford H (1957) A clinical and pathologic study of exfoliation of the lens capsule *Trans amer ophthal Soc 55* 189–216

Hørven I (1966) Exfoliation syndrome A histological and histochemical study *Acta ophthal (Kbh) 44* 790–800

Inomata H Bill A & Smelser G K (197?) Unconventional routes of aqueous humour outflow in cynomologus monkey (Macaca irus) *Amer J Ophthal 73* 893–907

Layden W E & Shaffer R N (19?4) Exfoliation syndrome *Amer J Ophthal 78* 835–841

Ringvold A (1970) The distribution of the exfoliation material in the iris from eyes with exfoliation syndrome (pseudoexfoliation of the lens capsule) *Virchows Arch Abt A path Anat 351* 168–178

Ringvold A (197?) Electron microscopy of the limbal conjunctiva in eyes with pseudo exfoliation syndrome (PE syndrome) *Virchows Arch Abt A path Anat 355* ?5–?83

Ringvold A (19 3) On the occurrence of pseudo exfoliation material in extrabulbar tissue from patients with pseudo exfoliation syndrome of the eye *Acta ophthal (Kbh) 51* 411–415

Ringvold A & Vegge T (19 1) Electron microscopy of the trabecular meshwork in eyes with exfoliation syndrome (pseudoexfoliation of the lens capsule) *Virchows Arch Abt A path Anat 353* 110–1?

Speakman J S & Ghosh M (19 6) The conjunctiva in senile lens exfoliation *Arch Ophthal (Chicago) 94* 175–1159

Sugar H S Harding C & Barsky D (19 6) The exfoliation syndrome *Ann Ophthal 8* 1165–1181

Tarkkanen A (196?) Pseudoexfoliation of the lens capsule *Acta ophthal (Kbh) Suppl* ?1

Thomassen T L (1949) On the so called capsular glaucoma *Acta ophthal (Kbh)* ? 423–42

Yamagishi N (19 ?) Pseudo exfoliation syndrome Trabeculotomy *Jap J Clin Oph thal 30* 33–40

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DEMONSTRATION OF PERIPHERAL HEMIOPIC BORDER STEPS BY STATIC PERIMETRY

BY

LARS DAMGAARD-JENSEN

10 normal eyes were examined by static perimetry along a horizontal line 60° below the fixation point All showed a greater sensitivity in the temporal hemifield The study confirmed the previously reported existence of a step and indicated a greater threshold specifically at the hemiopic border

Key words perimetry static – steps at the vertical meridian – field dominance temporal – normal eyes

In a previous paper (Damgaard Jensen 1977) the author focused attention on hemiopic differences in normal and glaucomatous eyes By kinetic perimetry it was found that even normals (about 50 %) may exhibit small steps at the vertical meridian The fields of normal eyes were always largest on the temporal side of the hemiopic line of the visual field If the opposite is the case this should be regarded as strong evidence of a pathological state

The aim of the present investigation was to study the retinal sensitivity on either side of the hemiopic border in the peripheral retina by static perimetry

Material and Methods

Ten normal right eyes (4 females 6 males age 20–35 years) were examined All eyes were emmetropic visual acuity was 1 0 and none of the examined persons exhibited clinical signs of CNS disease Static perimetry was carried out with a Goldmann

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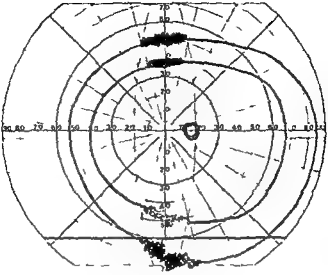

Fig 1

Normal visual field (kinetic perimetry) The line indicates the site of static perimetry used in this investigation

940 ST perimeter Minor adjustments enabled the examination of the peripheral field at a horizontal line 60 below the fixation point (cf Fig 1) All examinations were made in duplicate

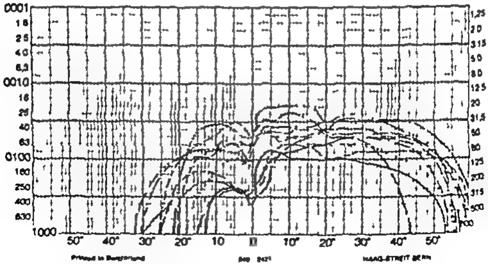

Fig 2

Ten static perimetries of normal eyes at a plane 60 below the fixation point Steps and dips at the zero line temporal field dominance

Results

All 10 eyes demonstrated a greater sensitivity in the temporal field than in the nasal one and a more or less pronounced reduction of sensitivity at the vertical meridian (Fig 2)

Discussion

This investigation confirms the existence of hemiopic disparities and steps The phenomenon is not due to any specific kinetic sense disparity between the two hemifields as the applied static technique may be considered a reliable means by which the retinal sensitivity can be tested Comparison between Fig 1 and Fig 2 makes it clear why the curves of the static perimetry reach much further temporally than nasally This only expresses the well known fact that the temporal field is larger than the nasal one The steep bend in all 10 curves of Fig 2 at the zero line however indicates a sudden change in light sensitivity at this site The dip at the zero line (higher threshold at the hemiopic line) might implicate that an additional factor is influencing the sensitivity at this site Animal experiments suggest overlapping of receptive fields 1–2° on either side the hemiopic line (for refs see Damgaard Jensen 1977) Fig 2 shows that the dip extends only about 2° to the temporal side as regards most of the examined eyes but is rather ill defined nasally The dip bears some resemblance to Ehlers two point discrimination examinations of normal eyes (for refs see Damgaard Jensen 1977) and the question arises whether the dips in Fig 2 reflect some inhibitory intracranial mechanism On examining the field at the vertical meridian minimal adjusting movements of the eye are likely to cause rapidly changing projection from one brain half to the other because of this overlapping

All 10 examinations were repeated once and a high degree of reproducibility was found except most peripherally Moreover the reproducibility corresponding to the dips was relatively small compared to the neighbouring more peripheral parts Three of the examines spontanously expressed great uncertainty during the examination of the parts at vertical meridian and the seven others readily confirmed the same phenomenon on direct questioning This is in good accordance with the finding of relatively great standard deviations on repeated plottings close to the vertical meridians in kinetic perimetry (Damgaard Jensen 1977)

Reference

Damgaard Jensen L. (1977) Vertical steps in isopters at the hemiopic border – in normal and glaucomatous eyes. *Acta ophthal. (Kbh.)* 55, 111–122

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POLYSACCHARIDE COATING OF HUMAN CORNEAL ENDOTHELIUM

BY

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Electron microscopy revealed the presence of a 600–1500 Å thick layer of polysaccharide on the surface of human corneal endothelial cells The surface layer was visualized by combined fixation and staining in a mixture of ruthenium red and osmium tetroxide The coating material was stable for at least 39 h post mortem and was retained on disintegrating cells

Key words cell coat – corneal endothelium – human cornea – mucopolysaccharide – ruthenium red – electron microscopy

Since the demonstration of mucopolysaccharide surface coatings on human vascular and peritoneal endothelial cells by McGovern (1956) and on the surface of more than 50 different cell types in the rat by Rambourg Neutra & Leblond (1966) several investigators have reported observations on mammals and birds pointing towards the presence of some substance on the posterior corneal surface At present very few data are available concerning the physical or chemical structure of such a coating material

Abelsdorff & Wessely (1909) found a viscous material occupying the main part of the anterior chamber of various owls Barany Berggren & Vrabec (1957) found an increasing density of the material towards the owl cornea and found that the material could be partially depolymerized by testicular hyaluronidase Vrabec (1957 1958) and Wolff (1968) obtained replicas of a layer on endothelial cells and observed silver

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impregnation of some substance on the posterior corneal surface. Speakman (1959a,b) found an osmium tetroxide positive layer on the posterior corneal surface in rabbit, cat and monkey which did not stain by traditional histochemical methods for identification of acid mucopolysaccharides. Iwamoto & Smelser (1965) observed that thorotrast particles clumped at some distance from the endothelial cell wall when injected into the anterior chamber of human eyes. Preziosi (1966) observed some substance covering the endothelial surface of Rhesus monkeys when viewed in phase contrast microscopy. Kirk & Hassard (1969) showed that the outline of endothelial cells in cat, ox and man could be brought forth under controlled osmotic and ionic conditions. They inferred that some substance coated the intercellular borders and suggested that an extension of the substance to the entire endothelial surface prevented the staining of dead feline endothelial cells by lissamine green. Hodson (1971) presented evidence of endothelial macromolecular synthesis by *in vitro* experiments with radioactively labelled glucose. During this study Harnish (1976) verified the presence of acid mucopolysaccharides on cells covering the trabeculum of human eyes by application of the ruthenium red osmium tetroxide technique introduced by Luft (1966). This study was undertaken after observations parallelling those reported by Preziosi (1966) in incident light and phase contrast microscopy on living bovine endothelial cells.

Material and Methods

The material comprised 11 normal human corneas from patients two days to 91 years old, fixed at various time intervals post mortem. Corneas were obtained after storage at 16–22°C for 8–10 h and at 4°C for the remaining post mortem time. One central corneal button with normal endothelial cells from a case of keratoconus and one central button from a normal cornea were prepared immediately after excision.

Luft (1966) introduced a technique by which some cell coats are made visible in light and electron microscopy by the coupling of ruthenium red and osmium tetroxide to acid mucopolysaccharides in the coat. The original technique of fixation in glutaraldehyde and ruthenium red prior to treatment by osmium tetroxide and ruthenium red was discarded after repeated failures of retaining the endothelial cells in contact with the membrane of Descemet. Combined staining and fixation was carried out by immersion of the tissue in equal parts of ruthenium red (1500 ppm in distilled water), 5% osmium tetroxide and 0.2 M cacodylate buffer (pH 7.3) for 1½ h at 25°C. After fixation the tissue was transferred to cacodylate buffer, dehydrated in graded ethanol to propylene oxide and embedded in epon. Some ultrathin sections were grid stained by uranyl acetate and lead citrate before examination in a Jeol 100 C microscope, other sections were examined without additional staining.

Results

When the tissue was fixed in ruthenium red osmium tetroxide a coherent deposit of osmium tetroxide appeared on the endothelial surface (Fig. 1).

In sections perpendicular to the cell wall (indicated by a distinct threelaminar cell membrane) the deposit measured between 600 and 1500 Å. Extensions

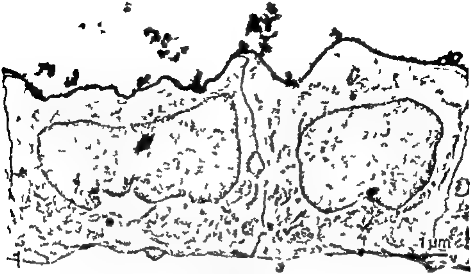


Fig 1
Cellular coating on endothelium from an infant aged 2 days Fixed 14 h post mortem in ruthenium red osmium tetroxide and contrast stained Magnification 6600 ×

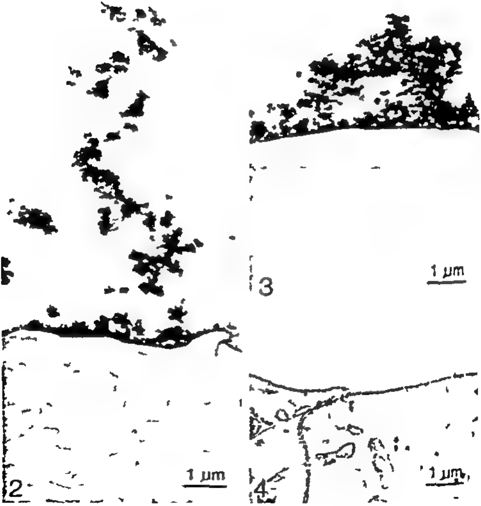
of the surface deposit reached the tight junctions No surface material was found in the intercellular spaces basal to the tight junctions Threadlike bran ching and coiled extensions of the deposit were found as far as 8 μm from the coherent surface layer (Figs 2 and 3) Only small amounts of electron dense material were found on the cell surfaces when ruthenium red was omitted from the fixative (Fig 4)

No time related change was noted in the density or in the configuration of the surface deposit The coating material was still present on the fragmented outer limiting membranes of disintegrating cells with gross degenerative changes (Fig 5)

Addition of ruthenium red to osmium tetroxide did not affect the pre servation of intercellular ultrastructure The ultrastructure of cells fixed in ruthenium red osmium tetroxide immediately post mortem appeared normal Endothelial cells fixed 8 to 39 h post mortem showed vacuoles in the cytoplasm mitochondrial swelling fragmentation of cristae and decreased density of the matrix material (Figs 1–4) In each cornea cells with only slight mitochondrial swelling as well as cells with clumping of nuclear chromatin endoplasmatic disorganisation and rupture of the limiting membranes were observed

The relation of the surface coating to the phenomenum of vacuolization

described by Kirk & Hassard (1969) was investigated A cornea obtained 14 h post mortem was bisected One half was fixed in ruthenium red osmium tetroxide (Fig 6) while the other half was immersed in 0 9 % NaCl for 10 min before fixation The vacuolization appeared by widening of the intercellular spaces between basal desmosomes and the tight junctions while the coating material was unchanged (Fig 7)



Figs 2–4

2 and 3 Extensions of the cellular coating on endothelium from a patient aged 50 years Fixed [illegible] h post mortem in ruthenium red osmium tetroxide Magnification 10 000
4 Endothelium from a patient aged 56 years Fixed 10 [illegible] post mortem in buffered osmium tetroxide and contrast stained Magnification 10 000

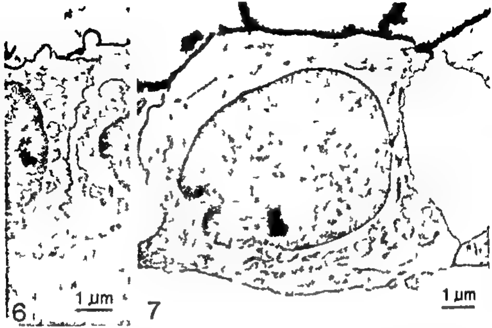
Fig 5

Cellular coating on a disintegrating cell from a patient aged 81 years Fixed 15 h post mortem in ruthenium red osmium tetroxide and contrast stained Magnification 20 000 ×

Comments

Ruthenium red is an ionic complex of ruthenium and ammonia The molecular weight is 860 and the net charge of the complex is +6 (Fletcher et al 1961) Ruthenium red precipitates a variety of negatively charged large polymers and fails to precipitate neutral polysaccharides and aliphatic compounds (Luft 1966) It stains pectin in plant tissue (Jensen 1962) bone matrix and interfibrillary substance in tendons (Heidenhain 1913) coating on intestinal microvilli (Luft 1964) and the cell coat of amoebae (Szubinska 1964) The amount of ruthenium red bound in precipitated polysaccharides does not increase the mass of the stained tissue components sufficiently to make it visible under the electron microscope In presence of osmium tetroxide a coupled reaction of acid polysaccharide ruthenium red and osmium tetroxide occurs (Luft 1966)

Mitochondrial disorganization cytoplasmatic vacuolization and clumping of nuclear chromatin were the only marked early degenerative changes Identical observations were reported by Shaeffer (1963) and Schultz (1971) in post mortem materials



Figs 6 and 7

6 Tightly adhering endothelial cells from an infant 2 days old Fixed 14 h post mortem in ruthenium red osmium tetroxide and contrast stained Magnification 8500 ×
7 Second half of the cornea in Fig 6 Preparation as in Fig 6 after 10 min in 0.9% NaCl Magnification 8500 ×

The photomicrographs obtained in this study shows coherent ruthenium red osmium tetroxide precipitates on the cellular surface forming a layer of 600-1500 Å and strings of precipitate extending as far as 8 µm from the surface This finding confirms the existence of a macromolecular layer coating the endothelial cells The photographs may represent the *in vivo* configuration of the coating material or they may picture a distorted and shrunken gel with an increasing density towards the surface of the cells similar to the gel found on the owl corneas (Barany Berggren & Vrabec 1957)

The finding of similar layers of coating material on cells fixed only seconds after removal from a living patient and on dead and disintegrating cells fixed hours after corporal death suggests that the coating material is stable for at least 39 h post mortem

At present the physiological role of this coating material is entirely unknown The presence of a presumably negatively charged layer on the surface of normal endothelial cells calls for revision of earlier estimates of ionic gradients across the endothelial cell membrane

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References

Abelsdorff G & Wessely K (1909) Vergleichend physiologische Untersuchungen uber den Flussigkeitswechsel des Auges in der Wirbeltbierreihe *Arch Augenheilk 64* Erganzungsheft 65–195

Barány E Berggren L & Vrabec F (1957) The mucinous layer covering the corneal endothelium in the owl Strix Aluco *Brit J Ophthal 41* 25–30

Fletcher J M et al (1961) Ruthenium Red *J chem Soc 9* 2000–2006

Harnish J P (1976) Elektronmikro kopische Darstellung saurer Mukopolysakkaride im Trabekelwerk *Klin Mbl Augenheilk 169* 90–94

Heidenhain M (1913) Über die Bearbeitung der Sehnen zu Kurszwecken insbesondere uber die Verwendung des Rutheniumrots und Malloryschen Bindgewebsfarbung *Z wiss Mikr 30* 161–167

Hodson S (1971) Makromolecular synthesis in corneal endothelium *Exp Eye Res 11* 15–19

Iwamoto T & Smelser K (1965) Electron microscopy of the human corneal endothelium with reference to transport mechanisms *Invest Ophthal 4* 270–284

Jensen W A (1962) *Botanical Histochemistry* Freeman San Francisco 1962

Kirk A H & Hassard D T R (1969) Supravital staining of the corneal endothelium and evidence for a membrane on its surface *Canad J Ophthal 4* 405–415

Luft J H (1964) Electron microscopy of cell extraneous coats as revealed by ruthenium red staining *J Cell Biol 23* 54A–55A

Luft J H (1966) Fine structure of capillary and endocapillary layer as revealed by ruthenium red *Fed Proc 25* 1773–1783

McGovern V J (1965) Mast cells and their relationship to endothelial surfaces *J Path Bact 71* 1–6

Preziosi V A (1966) An apparatus for phase contrast microscopic observation of viable corneal endothelium during freezing and thawing *Amer J Ophthal 69* 19–26

Rambourg A Neutra M & Leblond C P (1966) Presence of a cell coat rich in carbohydrate at the surface of cells in the rat *Anat Rec 154* 41–59

Schaeffer E M (1963) Ultrastructural changes in moist chamber corneas *Invest Ophthal 2* 272–282

Schultz R O (1971) Laboratory evaluation of cryopreserved corneal tissue *Trans amer ophthal Soc 69* 563–608

Speakman J (1959a) Endothelial cell vacuolation in the cornea *Brit J Ophthal 43* 139–146

Speakman J (1959b) Stain permeability and ultrastructure of the corneal endothelium *Arch Ophthal (Chicago) 62* 882–888

Szubinska B (1964) Electron microscopy of the interaction of ruthenium violet with the cell membrane complex of Amoeba proteus *J Cell Biol 23* 92A

Vrabec F (1957) The inner surface of the trabecular meshwork studied by a replica technique *Amer J Ophthal* 44 1–12

Vrabec F (1958) Studies on the corneal and trabecular endothelium *Brit J Ophthal* 42 529–534

Wolff J (1968) Inner surface of regions in the anterior chamber *Docum ophthal* ° 113–24

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THE APPEARANCE OF THE OUTFLOW APPARATUS OF THE EYE AFTER STAINING WITH RUTHENIUM RED

BY

IAN GRIERSON WILLIAM R LEE and SHAHIDA ABRAHAM

The outflow apparatus from adult baboon and rabbit eyes was stained with the inorganic dye ruthenium red The ruthenium reaction product coated the surface of the trabecular meshwork cells and the canalicular endothelial cells Deposits also impregnated the various connective tissue elements within the trabeculae and the extracellular spaces of the endothelial meshwork A fine fibrillar network could also be identified with ruthenium red and this was present in the trabecular cores and the extracellular spaces of the endothelial meshwork It was considered that the fibrillar network may represent a matrix of glycosaminoglycans and glycoproteins The significance of these materials in relation to aqueous outflow was discussed

Key words transmission electron microscopy – baboon – rabbit – outflow apparatus – ruthenium red – glycoproteins – glycosaminoglycans

The present ultrastructural investigation was conducted to determine the pattern of ruthenium red staining in the baboon and rabbit outflow apparatus Ruthenium red stains extracellular materials and is considered to have a particular affinity for glycosaminoglycans and glycoproteins (Luft 1964 1971a b)

Materials and Methods

The eyes from 5 adult baboons (*Papio anubis*) weighing between 16 and 25 kg and 5 adult pigmented dutch rabbits weighing between 1 8 and 2.5 kg provided the material for this study After enucleation each eye was bisected

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the lens excised and segments of limbal tissue were removed. Subsequently the majority of the tissue was immersed in 2.5 % glutaraldehyde buffered with 0.2 M sodium cacodylate which contained ruthenium red. The concentration of ruthenium red in the primary fixative was varied between 300 and 1000 p.p.m. The remaining segments of "fresh" limbal tissue were incubated at 37 C for periods between 30 min and 3 h in either a) buffered testicular hyaluronidase (B.D.H. Laboratories) of various activities between 100 and 2000 IU per ml or b) hyaluronidase inactivated by boiling. Thereafter the incubated tissues were also immersed in buffered glutaraldehyde which contained ruthenium red.

The segments of limbal tissue were trimmed down to blocks with a thickness of approximately 1 mm and then left for 2 to 12 h in the primary fixative solution. Subsequently the blocks were washed in cacodylate buffer, post fixed for at least 4 h in 2 % buffered osmium tetroxide and then rewashed in cacodylate buffer. Each solution contained the appropriate concentration of ruthenium red.

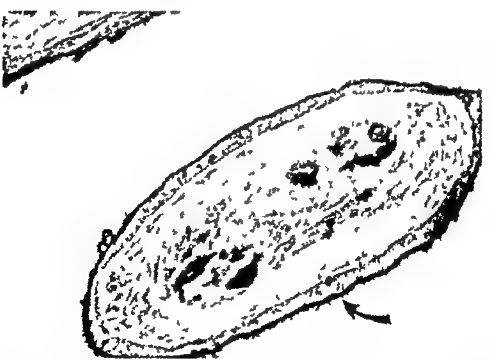

Fig. 1

Uveal trabecula from the outflow system of the baboon which has been treated with 1000 p.p.m. of ruthenium red. A rich electron-dense deposit of ruthenium red is adherent to the "free" or apical surface (arrow) of the endothelium on the trabecula. Uranyl acetate section staining (× 10,000).

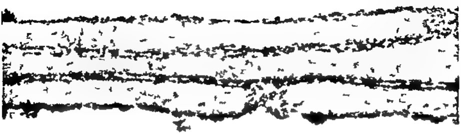

Fig 9
Process connections which link adjacent trabeculae in the corneoscleral meshwork of the baboon The tissue has been treated with 800 p p m of ruthenium red Deposits of electron dense reaction product fill the intercellular spaces No section staining (× 100 000)

Following fixation impregnation and washing the tissue was dehydrated through graded alcohols cleared with propylene oxide and embedded in Araldite The staining procedure which we adopted was adapted from that outlined by Luft (1964 1971a b) Thin sections (600–800 A) were cut on an L K B Ultrotome III and viewed in a Phillips 300 or 301 electron microscope either without subsequent section staining or after 10 min exposure to uranyl acetate solution

Results

The ruthenium red reaction product was identified as an electron dense homogenous material within the tissue blocks However even with a relatively loose structure like the trabecular meshwork the effective penetration of the stain was limited to a few microns beyond the cut surfaces of each segment Thereafter the distribution of the stain was patchy and deposits of ruthenium red were seldom found at the centre of a 1 mm thick block The investigation was therefore restricted to the periphery of the tissue blocks where a constant regular and reproducable staining reaction was present

An electron dense coating of ruthenium red covered the surface of the trabecular meshwork cells and canalicular endothelial cells in both the baboon and the rabbit As well as forming a deposit on "free" cell surfaces (Fig 1) ruthenium red penetrated intercellular spaces fairly readily (Fig 2) The thickness

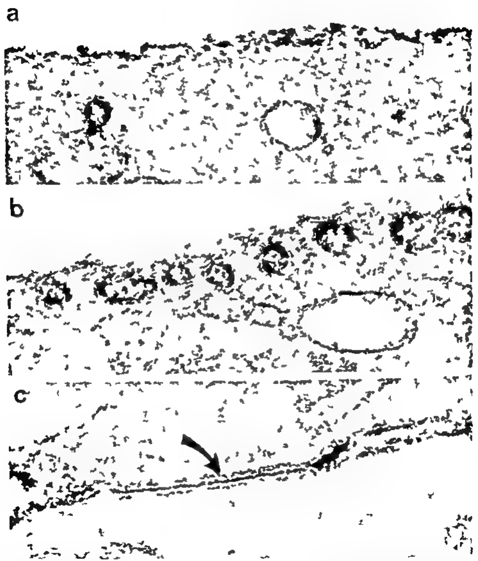

Fig 5

Meshwork cells from the baboon treated with 400 p p m of ruthenium red a At this concentration the surface layer on the meshwork cells is thin and discontinuous but there is selective staining for b) micropinosomes and c) the viable space (arrow) within the gap junctions which modify the intercellular clefts Uranyl acetate section staining ((a) 120 000 (b) 150 000 and (c) ?_0 000)

Fig 4

Part of a baboon corneoscleral trabecula stained with ruthenium red (1000 p p m) The basement material (BM) elastic like substances (E) and the collagen (arrow) are electron dense In longitudinal sections the periodicity in the collagen and the clumps of elastic like material is emphasised The insert shows collagen fibrils from a rabbit trabecula stained with ruthenium red (800 p p m) and cut in cross section Each fibril is surrounded with a coating of electron dense reaction product No subsequent section staining (x 54 000 insert x 100 000)

and intensity of the electron dense surface coat varied with the concentration of ruthenium in the fixative solutions At 300 and 400 p p m the ruthenium deposit was patchy (Figs 3a and b) whereas with stronger solutions of up to 800 p p m a regular and continuous deposit was observed (Fig 2) At the highest concentration (1000 p p m) the electron dense material formed a diffuse layer on the surfaces of the cells (Figs 1 and 4)

Fig

Shows some of the extra cellular constituents of a trabecular core in a rabbit which are stained with ruthenium red 800 p p m) Collagen fibrils can be seen both in cross section (small arrows and in longitudinal sections (large arrows) A network of fibrillar material connect the various collagen fibrils Uranyl acetate section staining

× 4 000

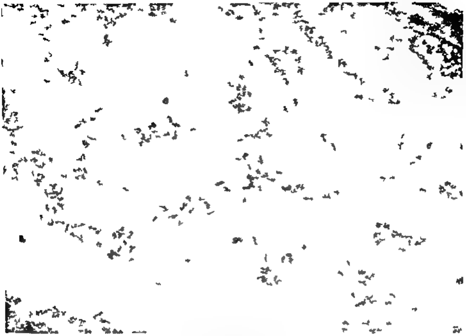

Fig 6

The network of electron dense material in the extracellular spaces of the endothelial meshwork after ruthenium red treatment (400 p p m) Baboon tissue no section staining (× 100 000)

With low concentrations of ruthenium red there was preferential staining for the interspaces of the gap junctions and maculae adhaerentes which were sometimes found between adjoining baboon and rabbit meshwork cells (Fig 3 c) In addition deposits were found selectively on the limiting membranes of micro pinosomes where these vesicles opened onto the surface of meshwork and canal endothelial cells (Fig 3 b)

Ruthenium red increased the electron density of the connective tissue elements in the trabeculae (Fig 4) The basement layer had an increased electron density and generally had a more granular appearance than in conventionally stained material When the elastic like material and the collagen of the trabecular core was cut longitudinally ruthenium red emphasised the banding pattern in both materials In cross section the elastic like substance and each collagen fibril was seen to be surrounded by an electron dense deposit of ruthenium red (Fig 4) The various connective tissue elements in the trabeculae were sometimes seen to be connected by a web or network of fine filamentous material (Fig 5)

The extracellular spaces of the endothelial meshwork had a particular affinity for ruthenium and this fine grain deposit demarcated an even more delicate network of interconnecting filaments than that present within the trabeculae (Fig 6) The network extended between neighbouring cells and enmeshed the aggregates of collagen curly collagen and elastic like material To see the net work to its best effect the concentration of ruthenium red in the fixative solu tion had to be low otherwise the fine filaments were obscured by electron dense stain deposits

Ruthenium formed a surface coat on the endothelial cells which surrounded Schlemm s canal The layer was thicker on the luminal than the trabecular aspect of the endothelium The material also covered the limiting membrane of giant vacuoles and penetrated the lateral cell borders to the level of the intercellular junctions

The chemical nature of the ruthenium positive material which was present in the outflow apparatus was not determined After incubating blocks of fresh tissue in active hyaluronidase the staining reaction was less pronounced but in addition incubation in boiled hyaluronidase also produced an effective re duction of the subsequent staining reaction It would appear that either a) the pretreatments had adverse effect on the staining mechanism or b) the hyaluroni dase molecule in its deactivated form had a masking effect

Discussion

Luft (1964 1971a b) proposed that ruthenium red binds to the polysaccharide moieties of glycosaminoglycans and glycoproteins but the evidence presented by this author was somewhat circumstantial and the precise nature of the reac tion remains obscure In the present study ruthenium red was used to stain the outflow apparatus in both the baboon and the rabbit Although enzymatic treatment was found to be unhelpful the similarity of the staining pattern produced in the outflow apparatus with ruthenium compared to that produced by other cationic staining systems (Segawa 1970 Armaly & Wang 19 5 Grier son & Lee 1975) makes Luft s proposals seem reasonable

Ruthenium red has the particular advantage a) of fine resolution and accurate location and b) its staining reaction takes place at physiological pH levels The major disadvantage of the material is its extremely poor penetration into tissue blocks Because effective staining is limited to only a few microns of surface tissue comparative investigations using this dye are fraught with difficulty

Recently Segawa (1975) has shown that an extremely intense ruthenium staining reaction can be produced in the endothelial meshwork of patients suf fering from primary open angle glaucoma The staining reaction in these patients

appeared to be more extensive than that found in either the baboon or the rabbits of the present study Segawa found that the ruthenium positive material was far more sensitive to chondroitinase ABC than to streptomycetes hyaluronidase therefore the material was thought to be sulphated polysaccharides rather than hyaluronic acid It must be borne in mind that Segawa used trabeculectomy specimens as the main source of his tissue Cellular damage due to surgical manipulation is a hazard association with trabeculectomy specimens (Lee & Grierson 1974) and the possibility exists that some of the increased staining could be due to extruded cytoplasmic polysaccharides rather than extracellular glycosaminoglycans (Luft 1971a)

Probably the most significant findings of the present investigation is the demonstration of a delicate fibrillar network in the trabecular and endothelial meshwork It is considered that this may be a framework of glycosaminoglycans or glycoproteins Such a framework would be of particular importance in the extracellular spaces of the endothelial meshwork which are the narrowest and most tortuous portion of the outflow pathway The fine polysaccharide mesh would help to bind cellular and extracellular elements together have a selective filtration effect on the passage of solute molecules and because the polymers are strongly hydrophilic they will bind water into the tissues (Ogston 1970) Thus the distribution and density of the mucopolysaccharides will influence both the general conductance of aqueous humour through the system and the direction of fluid movement to the canal endothelium

Acknowledgments

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References

Armaly M F & Wang Y (1975) Demonstration of acid mucopolysaccharides in the trabecular meshwork of the rhesus monkey *Invest Ophthal 14* 507–516

Grierson I & Lee W R (1975) Acid mucopolysaccharides in the outflow apparatus *Exp Eye Res 21* 417–431

Lee W R & Grierson I (1974) Relationships between intraocular pressure and the morphology of the outflow apparatus *Trans ophthal Soc U K 94* 430–449

Luft J H (1964) Electron microscopy of cell extraneous coats as revealed by ruthenium red staining *J Cell Biol 23* 54a

Luft J H (1971a) Ruthenium red and violet I Chemistry purification methods of use for electron microscopy and mechanism of action *Anat Rec 171* 347–368

Luft J H (19 1b) Ruthenium red and violet II Fine structural localisation in animal tissues *Anat Rec 171* 369–416
Ogston A G (1970) The biological functions of the glycosaminoglycans In *Chemistry and Molecular Biology of the Intercellular Matrix* (Balazs E A Ed) Vol 3 p 1 31 Academic Press London
Segawa K (1970) Localisation of acid mucopolysaccharides in the human trabecular meshwork *J clin Ophthal (Jap) 24* 363–367
Segawa K (1975) Ultrastructural changes of the trabecular tissues in primary open angle glaucoma *Jap J Ophthal 19* 317–335

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COMPUTER TEST LOGICS FOR AUTOMATIC PERIMETRY

BY

ANDERS HEIJL

Using an automatic computerized perimeter developed by Heijl & Krakau (1975b) three different perimetric test logics one simple (I) and two more complicated and time consuming (II & III) were investigated in practical experiments on healthy normal test subjects and patients and in computer simulated tests The patients either had a verified diagnosis of glaucoma or glaucoma was suspected

The best consistency in measured thresholds was obtained with test logic II in which an averaging procedure is used The variation of the results was larger in pathological than in normal visual fields

All test logics investigated readily detected the pathological field defects but blind spots could easier pass unrecognized with the simplest logic than with the other two logics

The conclusion is drawn that a simple test logic can be used for perimetry in glaucoma suspects if no visual field defect has previously been documented For the follow up of pathological fields a fairly complicated test logic e g using averaging is preferable

Key words automatic perimetry – visual fields

We have earlier presented a fully automatic perimeter primarily intended for glaucoma visual field screening and control (Heijl & Krakau 1975b) A test logic for glaucoma visual field screening has also been constructed and used in a clinical study (Heijl 1976) We have not however presented figures for the reproducibility of thresholds measured by this perimeter

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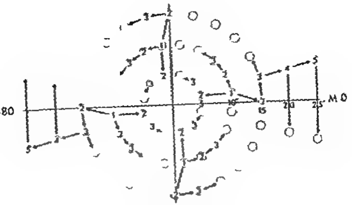


Fig. 1

Test point pattern of the perimeter. Each test point is marked by a circle. Points marked 1 are first tested. Their thresholds are then transferred to points marked 2 etc.

In a paper on a simple prototype perimeter various test logics were dealt with (Heijl & Krakau 1975a). A staircase mode of testing with steps of constant size was found suitable. This means that when a patient perceives a stimulus at a certain point the next testing of that point is performed with a lower intensity and vice versa. In this way an intensity level is reached at which the patient no longer perceives the stimulus, or, if the testing starts at subliminal intensities, a level strong enough to be seen is eventually reached. If the testing is continued, the resulting process will fluctuate between levels where the probability of seeing is 1 and 0. In the mentioned paper, different ways to bring the test process to an end and to decrease the dispersion of the test results were discussed, provided the patient did not appreciably change his threshold during the test.

Starting off from these results, a few test logics intended for the present apparatus were constructed. The aim of the present study is to analyse how these logics turn out when applied to normal subjects and patients. Our interest is focused on the reproducibility and the ability to detect visual field defects.

Methods

The automatic perimeter used (Heijl & Krakau 1975b) has 64 static stimuli (light emitting diodes) covering the central visual field. The stimuli can be exposed at 16 intensity levels. The ratio between two consecutive levels is 1.?

Computer test logic

Three different perimetric test logics were compared – one fairly short (Test logic I) and two longer (Test logics II and III) They were all executed at one test session the short test logic constituted the first part of the test session This is an advantage since if the patient cannot achieve his usual level of performance at one test session this will most likely affect results from all the three test logics

The specifications of the computer test logic used were

a All 64 test points were used The positions of these are shown in Fig 1

b Another stimulus was exposed in the patient s blind spot area at random intervals This served as an indicator of the patient s fixation Obviously if the patient correctly maintained fixation this light could not be seen

This stimulus was so programmed as to be shown on an average 1/9 of the total number of presentations The number of patient answers to this stimulus and the total number of blind spot stimulus presentations were stored by the computer for the short and the full test session respectively

c During the test session all points under testing were shown in random order In that way the patient could not anticipate where the next stimulus was to appear

d The threshold was determined by an up and down staircase method (Fig 2) If a test point n was illuminated at an intensity i and the patient perceived the light

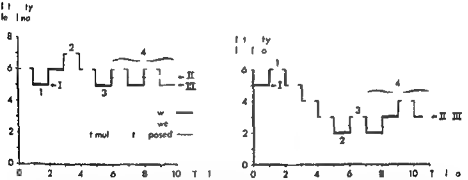
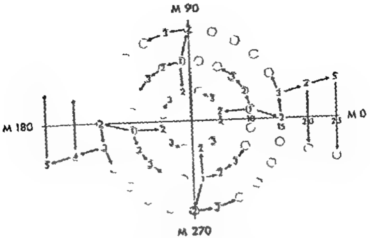


Fig 2 A and B

Examples of test procedures at one single point Stimulus intensity level number increases (i e stimulus intensity decreases) with every answer from the patient (thick horizontal lines) and decreases when no answer is given (broken horizontal lines) 1 2 and 3 denote the first second and third [illegible] of sign respectively 4 denotes the four intensity levels the mean of which forms threshold II The last stimulus of the curves (dotted broken line) [illegible] answer [illegible] this stimulus does not influence the calculation of threshold II I II and III denote thresholds I II and III



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Starting off from these results a few test logics intended for the present apparatus were constructed The aim of the present study is to analyse how these logics turn out when applied to normal subjects and patients Our interest is focused on the reproducibility and the ability to detect visual field defects

Methods

The automatic perimeter used (Heijl & Krakau 1975b) has 64 static stimuli (light emitting diodes) covering the central visual field The stimuli can be exposed at 16 intensity levels The ratio between two consecutive levels is 1 2

Presentation of results

1 When the test was completed the total number of stimulus presentations the number of blind spot stimulus presentations and the number of answers on blind spot stimulus presentations were printed out on the teletype for the short and the long tests respectively The visual field charts obtained by the different test logics were plotted on a graphic plotter using the system described by Heijl & Krakau (1975b)

The test logics were mainly based on our earlier experience with automatic perimetry Some guidance was obtained from computer simulated tests

In such tests Test logic I was compared with two other logics – one very simple (A) in which the first change of sign determined the threshold and one (B) in which the third change of sign preceded the threshold determination The simulations showed that Test logic I should give better reproducibility in threshold measurements and better ability to detect visual field defects than Test logic A but not as good as Test logic II Test logic II is much more time consuming than Test logic I (roughly two extra stimulus presentations are needed at each test point) while logic I usually requires only a little more time than logic A Therefore Test logic I was considered a suitable short logic for the practical experiments

Experiment

Computer simulations

In the test logics described the test process will be governed by the set of transition probabilities ($p_{i,j}$) which exist between the different stimulus intensity levels The transition probability ($p_{i,i+1}$) between intensity level i and the next fainter level $i+1$ equals the probability of seeing of level i The transition probability towards the next stronger level ($p_{i,i-1}$) equals $1-p_{i,i+1}$ These probabilities vary with the intensity level and at each test point there is in principle one faintest level (i_k) where $p_{k,k-1}$ is 1 (except in some scotomatous areas) and one strongest level (i_l) where $p_{l,l+1}$ is 0 The interval from i_k to i_l can be denoted the threshold zone If a repetitive up and down staircase testing such as those described is allowed to continue if the transition probabilities remain stationary and if the test subject does not make any false answers the test process will behave as a Markov process (random walk) with reflecting barriers at i_k and i_l The mean of the levels visited will approach a fixed value determined by the transition probabilities Providing the conditions above are fulfilled threshold II constitutes a mean of an early part of such a Markov process

If false negative (fn) or false positive (fp) answers appear the transition probabilities will be changed and a new set of such probabilities ($p'_{i,i+1}$, $p'_{i,i-1}$) results

$$p'_{i,i+1} = p_{fp} + (1 - p_{fp} - p_{fn}) \times p_{i,i+1}$$
$$p'_{i,i-1} = p_{fn} + (1 - p_{fp} - p_{fn}) \times p_{i,i-1} = 1 - p'_{i,i+1}$$

Reasonable transition probabilities for one test point were fed into the computer together with different mean frequencies of false answers This formed the statistical patient model on which the different test logics were tried in computer simulated tests Starting from a predetermined intensity level the computer performed 1000 threshold determinations using the statistical model instead

of a patient and frequency distributions of the resulting thresholds were obtained for the different test logics

A few different sets of transition probabilities and frequencies of false answers were used and the starting point of the test process relative the threshold (as determined by the transition probabilities) was varied

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Fig 3

Frequency distributions of thresholds obtained through computer simulations The arrow shows the starting point of the test procedure Frequencies of false negative and false positive answers are given in the figures The mean of thresholds II is generally roughly half an intensity step higher than those of thresholds I and III This is to be expected since thresholds I and usually III are based on a last perceived stimulus while thresholds II are the mean of four stimulus exposures seen as well as not seen The results of test logics I II and III are marked as in Fig A

Transition probabilities for the intensity levels (without false answers) Fig A B C

$p_{01} = p_{12} =$	$p_{\;r} = 1$		
$p_{67} =$	0 99	$p_{9\,10} =$	0 1
$p_{\;8} =$	0 9	$p_{10\,11} =$	0 01
$p_{89} =$	0 5	$p_{11\,1} = p_{1\;13} =$	0

$p_{i\;1}$ and $p_{i\;\;1}$ (transition probabilities with false answers taken into consideration) are calculated by the computer according to the formulae on page 19

Fig D E $\quad p_{01} = p_{12} = p_{\;3} \;\; = 0 \qquad p_{01} = p_{1\,2} = p_{\;3} \;\; = 0\,05$

Fig 3 A

Test process starts at the 50 % threshold No false answers The distributions of thresholds I and III differ only slightly Thresholds II show the narrowest distribution

Fig 3 B

Test process starts a few steps away from the true threshold No false answers All distributions are somewhat displaced in the direction of the starting point Thresholds I are most affected

Fig 3 C

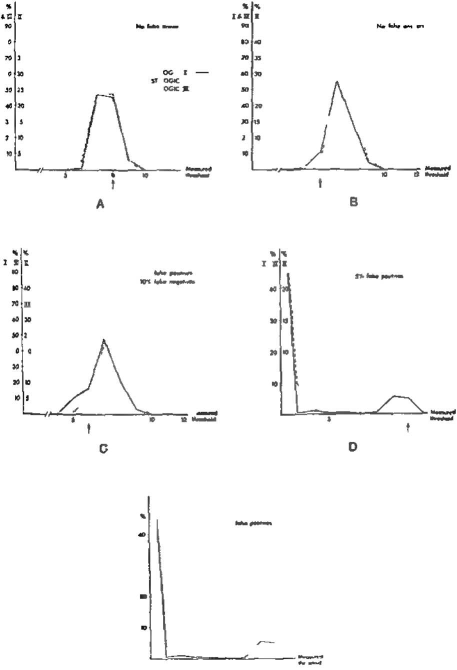
Test process still starts a few steps from the true threshold (same starting point as in B) False answers occur The distributions are broader than in B Test logic I is most affected

Fig 3 D

Test process starts many steps away from the true threshold which is 0 (as in a scotoma) False answers occur Sometimes obtained thresholds are incorrectly low Thresholds I are more often wrong than thresholds II and III

Fig 3 E

Same test situation as in D The full drawn line shows the distribution of thresholds I (the same distribution is shown in D) The broken line shows the distribution of thresholds I obtained in the second point inside the scotoma when the starting point of the test process is the threshold measured at the first point (full drawn line) The risk of ending at a too low threshold decreases considerably at the second point



A B C D E

Measurements on test subjects

Material Two groups of test subjects were used

1 Five healthy young normal test subjects (age ≤ 30 years) – mean age 27 years

2 Eight patients – mean age 62 years All patients either had a verified diagnosis of glaucoma or glaucoma was suspected (raised intraocular pressure cupped discs) In five of the eyes analysed there were visual field defects confirmed at an earlier date by automatic and conventional perimetry

Only one eye was tested in each subject

The normal test subjects mostly had a very limited experience of automatic perimetry All the patients had been subject to automatic perimetry but none of them were trained

Procedure Each test subject was tested five times The tests were often carried out in the course of one day – allowing a rest period of at least one hour between the sessions Not more than three consecutive days were used in any subject

The glaucoma patients did not receive any miotic therapy when the tests were carried out Only small changes of pupillary diameter and intraocular pressure wer encountered during the test period

Before the test was started the blind spot stimulus was so adjusted as to fall in the blind spot area of the eye to be tested The subject was instructed to keep his gaze steady on the fixation spot and to press his button when perceiving a stimulus The experiments were carried out at a background luminance of 1 0 cd/m except in two miotic patients in whom 0 1 cd/m was used The background luminance was kept constant for all five test sessions in each subject Stimulus exposure time was 0 5 sec and interstimulus interval 2 0 sec if the patient did not press his button In the case of an answer from the patient a new stimulus was shown after an interval of 0 5 sec All the subjects were corrected for ametropia and for near vision The duration of the first part of the test and of the full test was measured

Results

Computer simulations

Test logics I and in most cases III use a last perceived stimulus level for threshold determination The essential difference between these two logics is the number of changes of sign in the test process and the number of exposures before the threshold is determined Test logic III requires many more stimulus presentations than logic I at least three and usually five or more for each test point

Table I

Mean standard deviation of the measured thresholds for all test subjects N denotes healthy normal test subject P denotes patient

Subjects with normal visual fields			Mean standard deviation of measured thresholds (intensity steps)			Subjects with pathological visual fields			Mean standard deviation of measured thresholds (intensity steps)		
			Test logic						Test logic		
		Age	I	II	III			Age	I	II	III
S H	N	[illegible]	0.57	0.46	0.5[illegible]	C M	I	69	0.92	0.64	0.90
L G	N	97	0.69	0.55	0.61	M I	P	49	1.04	0.73	0.77
G Γ	N	98	0.79	0.50	0.64	G V	P	70	1.09	0.89	0.91
A H	N	30	0.40	0.30	0.35	T S	I	67	1.14	0.85	0.99
H S	N	96	0.63	0.55	0.67	G H	P	65	0.98	0.[illegible]2	0.90
M D	P	[illegible]9	0.[illegible]0	0.[illegible]8	0.69						
M B	P	[illegible]	0.51	0.39	0.41						
M H	P	61	0.36	0.33	0.47						
Mean			0.[illegible]9	0.46	0.55	Mean			1.01	0.[illegible]7	0.94

For an observer who never gives any false positive or false negative answers the distribution of the threshold determinations obtained by these two logics will differ only slightly as long as the starting point of the test process is close to the 50 % threshold (Fig 3 A) The averaging test logic II will show a narrower distribution of threshold determinations (Fig 3 A)

As soon as the test process starts one or more steps away from the true threshold the distributions of the threshold determinations will tend to be somewhat displaced in the direction of the starting point of the test (Fig 3 B) This displacement is more pronounced when test logic I is used and smallest when III is used The variation of the results obtained will usually also increase but the variation of test logic II will still be smaller than with the other test logics As long as no false answers are produced the displacement of the mean threshold obtained and the variation of the threshold determinations will not increase further when the starting level of the test process is moved outside the threshold zone

When false answers appear the standard deviations of the thresholds obtained with the different test logics increase The increment of the standard deviation will generally be most pronounced in the results of Test logic I and smallest in the results from Test logic II (Fig 3 C)

The most critical test situation appears when the test process starts a couple of steps away from the patient's threshold zone" and false answers occur Such a situation is present e g when a test point in a scotoma is tested in an unreliable patient The starting point of the test process is a fairly normal threshold transferred from a neighbour point The effect of false answers will be most pronounced in the results of Test logic I where often only one change of sign precedes the determination of the threshold Hence the faulty displacement of the mean recorded threshold in the direction of the starting point of the test process will be more pronounced when Test logic I is used than when the two other test logics are used in which at least three changes of sign precede the determination of the threshold (Fig 3 D)

The risk of ending at a too low threshold in an area with a very high threshold (such as a scotoma) decreases very much in the second point tested inside this area (Fig 3 E) since the threshold as measured in the first point is transferred to the second point and is used as the starting point for the test process there

Measurements on test subjects

The duration of the full test sessions containing all three test logics was found to range between 17 83 and 22 70 min (mean 20 38 min) The difference in mean duration between the patients and the normal subjects was only 0 71 min

The first part of the test in which Test logic I is completed ranged from [illegible] 38 min to 11 38 min (mean 8 59 min) For the short test logic the mean duration was 1 06 min shorter in the group of normals than in the group of patients The number of stimulus exposures ranged between 200 and 309 (mean 256) for the short test (I) and from 573 to 652 (mean 609) for the long test (Test logics II and III) With the short logic the mean number of exposures per session was 10 % larger in the patient group than in the group of normal subjects but the means of the two groups were almost identical for the long test For all the test logics the number of stimulus presentations were very close to 30/min

Reproducibility

The standard deviation of the results of the five consecutive measurements was calculated for all the 64 points tested in each subject (Table I) This deviation was significantly smaller with test logic II than with test logic III (sign test $P < 0\ 001$) Test logic III showed a somewhat smaller variation than the short test logic I (sign test $P < 0\ 05$) The difference in the results of the various test logics was more obvious when looking at ranges instead of standard deviations

Test points where the range of the five repeated measurements was large (arbitrarily ≥ 4 intensity levels) were counted The number of such points was significantly reduced (by 62 %) when test logic II was used as compared with the short test logic I (sign test $P < 0\ 001$)

The mean standard deviation of the measured thresholds was calculated for test points located at different eccentricities It was significantly smaller (≈ 30 %) in the central (5) than in the more peripheral (15–25°) test points (Student s t test $P < 0\ 05$)

This calculation was performed with normal visual fields only and as it was established that the variation was larger near to scotomas (see below) all test points were omitted which were located at the meridians 45° above or below the blind spot or closer to the horizontal meridian at the 15° circle

Furthermore the variation of the test results was significantly smaller in the normal visual fields than in the eyes with pathological visual fields (Wilcoxon s two sample test $P < 0\ 01$ for all three test logics) This is true despite the fact that many points in pathological visual fields were located in scotomas where the measured threshold was 0 and the variation small

The variation was larger in test points situated near scotomata than at other points (Student's *t* test $P < 0.05$).

The mean range of the test results of the two test points on the border of the scotoma but outside this scotoma (scotoma arbitrarily defined as test points where the mean threshold < 1) were compared to the mean threshold range of the results of all other test points at the same eccentricity in the same subject.

Ability to detect field defects

No difference in the frequency of missed blind spots was found between the different test logics if a blind spot was considered missed when no test point of the blind spot area appeared at zero level in the visual field chart. However if another criterion was used – the blind spot was considered missed only if no test point in the blind spot area showed a threshold < 3 – such misses were more frequent in the results of Test logic I (five charts out of 65–7.7 %) than in the results of the other two test logics (five charts out of 130–3.8 %). A blind spot which is missed when the second of these criteria is used can easily be overlooked in a field chart.

When this criterion was used it was found that four out of five blind spots missed in the charts of Test logics II and III were derived from one single test subject, a subject showing poor fixation which was even worse for the second part of the test than for the first. In such a case the measures taken against losses of scotomata in Test logics II and III cannot be expected to work.

No difference in the ability to detect pathological visual field defects could be seen when the results of the different test logics were compared. All the 75 visual field charts of the pathological eyes clearly showed defects and the defects were generally roughly the same size regardless of the test logic used. However in some subjects there was a tendency for the visual field defects to be somewhat larger in the charts of the time consuming Test logics II and III than in the results of Test logic I.

Discussion

The statistical model we have used for the computer simulations is based on the existence of a set of stationary transition probabilities. This idealization is reasonable in normal cases, but as has been shown (Heijl 1977) a considerable threshold increment sometimes exists during continuous automatic perimetry, mostly in pathological visual fields. Since cases with field defects are those which attract our attention to a great extent, the value of the simple model is limited. Certainly allowance for changes in the transition probabilities might

be made but since the extent of such changes can only be guessed they vary greatly from one patient to another and even between different retinal points in the same patient we are left with a model without the necessary simplicity and therefore of limited value Other objections might be raised to the statistical model It is possible for instance that the patient's response to a certain stimulus depends on the technique of testing – a test logic where a large number of subliminal stimuli are presented may discourage the patient and decrease his alertness Also a patient may use other criteria for what he regards to be a seen stimulus when a threshold stimulus immediately follows on a very supra liminal stimulus than if all stimuli presented are of roughly the same sub jective brightness

Although we thus adopt the view that computer simulations have a limited value and that results of measurements on patients must be the main guide in a search for appropriate test logics the simple model we have adopted can help us understand and predict the effect of various test logics provided the limitations mentioned are kept in mind

In all cases except two we found that the *variation* in threshold determinations at repeated testing was smallest when logic II and greatest when logic I was applied This was in accordance with the results of the simulations When introducing probabilities deduced from a frequency of seeing curve for un trained subjects (Greve 1973) in computer simulations the resulting dispersion was found to be close to the mean dispersion obtained in the normal visual fields in this study The dispersions of this study were of the same magnitude as those found by Bebie et al (1976) and those measured earlier by us (Heijl & Krakau 1975a) The dispersion represents a real variation in the results of the threshold estimation and are not due to a change of the mean threshold – a general constriction or widening of the visual field – between the test sessions

It may also be pointed out that Test logics II and III might have given even less dispersion provided thresholds II or III respectively had been transferred from the neighbour point to be used as starting level for the test process instead of threshold I However then the advantage of obtaining three different thresholds from one test session would have been lost

The existence of false answers is the main reason for the need of more or less sophisticated test logics Without false answers a most uncomplicated logic had been sufficient to reach the threshold zone (but an averaging test logic should still be able to narrow the distribution of the thresholds obtained) Since an erroneous answer may occur at any trial the risk of ending at a wrong level increases with the number of trials needed to reach the threshold This is the reason for our discussing at first error and second error in our first paper on perimetric test logics (Heijl & Krakau 1975a) The harmful effect

of these false answers is generally small if the error is made after presentation of a stimulus which is close to the true threshold Therefore by allowing the measured thresholds to spread to neighbour points and be used as starting levels for the test process in these points we not only reduce the number of stimuli that have to be exposed before the threshold is determined but also limit the effect of false answers Still false answers imply a danger in areas of the visual field where there are large threshold gradients such as occur on the borders of a scotoma Thus the harmful effect of false positive answers was seen not only in computer simulations but also e g in blind spot areas of the field charts Blind spots were sometimes missed in the field charts and it was found that blind spots were more often unrecognizable in the results of Test logic I than in the results of the other two logics just as could be expected from the results of the computer simulations We cannot however distinguish false positive answers due to erroneous fixation from such answers due to the test subject pressing his button without seeing a stimulus The existence of false negative answers could also be seen in some charts where the measured thresholds were falsely high at certain points close to the blind spot At such points strong intensity levels (transferred from the blind spot) had been used as starting points for the test process As expected thresholds I were more often erroneus in such points than thresholds II and III

Time dependent threshold deterioration did not disturb the testing in any of the subjects of this study to such an extent that the time consuming averaging Test logic II showed larger variation than Test logic I This might seem astonishing as threshold increments of magnitude 6 dB have been found to be fairly common at some retinal points during roughly 30 min of continuous automatic perimetry (Heijl 1977) However in the first place the period of time between the presentation of the stimuli used for the determination of thresholds I and II was generally only about 10 min Secondly time dependent threshold increments could be seen in the results Thus in the pathological visual fields thresholds III were generally higher than thresholds I (the mean threshold increment per min in this group was actually close to that found in a similar group in the study mentioned) while no difference between these thresholds could be seen in the normal fields Also field defects sometimes appeared to be larger in the charts of Test logic II and III than in the charts of Test logic I

With all test logics the standard deviation of the threshold determinations was larger in pathological visual fields than in normal fields Certainly the threshold variation at the borders of visual field defects was larger than in other areas of the pathological fields but even in normal points in pathological fields the thresholds measured showed larger variation than in normal

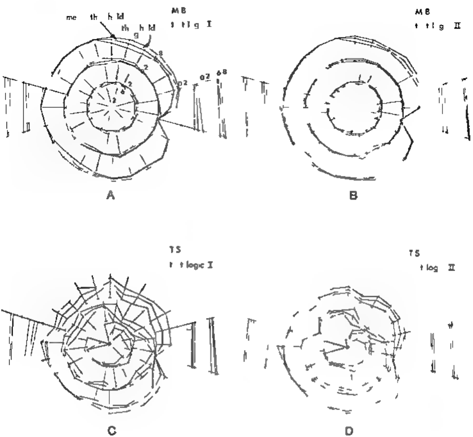


Fig 4

Visual field charts Results are plotted as polar coordinates (*not* as isopters) The intensity level of each test point is plotted on a scale through the test point In Fig A intensity level numbers are marked along the 45° and 15° meridians

In each chart the mean of the thresholds measured in five test sessions is shown together with the threshold range

In Figs 4 A and B many thresholds are so low that they have been plotted outside the scales

A Normal field Test logic I
B Normal field Test logic II
C Pathological field Test logic I
D Pathological field Test logic II

fields The mean age of the patients with pathological visual fields was higher than the mean age of the normal subjects but only six years higher than the mean age of the patients with normal fields These latter patients showed roughly the same variation as the young normals but much less than that present in the pathological fields Thus we do not believe that the higher variation of the pathological visual fields depends on age alone The simplest Test logic (I) generally showed better reproducibility in normal fields than the complicated Test logic II could achieve in pathological fields (compare Figs 4 A and 4 D)

No difference in the *ability to detect pathological visual field defects* was found when the results of the different test logics were compared Although often small the defects were readily detectable in all charts regardless of the test logic used However the observations on the missed blind spots as well as the computer simulations indicate that very small field defects should more safely be detected by the time consuming Test logics II and III than by a cruder logic but as soon as a defect is large enough to cover two consecutively tested neighbour points the probability for the defect to escape detection should decrease drastically even if the simple Test logic I is used in a subject producing a fairly large percentage of false answers (Fig 3 E) It might be pointed out here that field defects spotted in manual perimetry are very seldom so small as to comprise only one of the test points of our perimeter As a matter of fact we have seen no confirmed glaucomatous field defect detected by manual perimetry which have not been large enough to cover at least two test points in our perimeter

From the results the *general conclusion* is drawn that it is practical and justified to use a short and fairly simple test logic (such as Test logic I) for the examination of visual fields in glaucoma suspects which have not previously been examined or which were normal on previous examinations When it comes to a follow up of pathological visual fields maximal reproducibility is desirable Then a test logic using averaging or a similar procedure (such as Test logic II) is advantageous

References

Bebie H Fankhauser F & Spahr J (1976) Static perimetry accuracy and fluctuations *Acta ophthal (Kbh) 54* 339–348

Greve E L (1973) Single and multiple stimulus static perimetry in glaucoma the two phases of perimetry *Docum ophthal 36* p 141

Heijl A (1976) Automatic perimetry in glaucoma visual field screening A clinical study *Albrecht v Graefes Arch Ophthal 200* 21–37

Heijl A (1977) Time changes of contrast thresholds during automatic perimetry *Acta ophthal (Kbh) 55 ??*

Heijl A & Krakau C E T (1975a) An automatic static perimeter design and pilot study *Acta ophthal (Kbh) 53* 293–310

Heijl A & Krakau C E T (1975b) An automatic perimeter for glaucoma visual field screening and control Construction and clinical cases *Albrecht v Graefes Arch Ophthal 197* 13–?3

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A NOTE ON FIXATION DURING PERIMETRY

BY

A HEIJL and C E T KRAKAU

Small eye movements in the direction of the disappearing stimulus can be observed at kinetic perimetry when the test object enters a scotomatous area These may be responsible for the fact that several field defects missed at routine manual perimetry are spotted at automatic perimetry In the latter case the patient cannot predict the position of next test light since these are illuminated at random whereas at kinetic perimetry they are exposed in systematic order

By using two specially designed logics in automatic perimetry it was shown that there may be a reduction of the scotoma size if the lights are exposed in an ordered sequence This effect is avoided by using a logic with randomly exposed stimuli It is most likely that the difference can be attributed to malfixation

Key words perimetry – kinetic perimetry – automatic perimetry – fixation.

In a recent study on glaucoma screening (Heijl 1976) it was shown that many visual field defects previously missed at routine perimetry kinetic or the Armaly technique (Armaly 1972) were detected by automatic perimetry

In a previous paper on an automatic perimeter (Heijl & Krakau 1975b) a few glaucomatous field defects were used to illustrate the performance of this instrument It was then observed that the defects sometimes seemed larger and/or deeper when plotted by the automatic device than with kinetic perimetry

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A difference between the automatic and the manual test which perhaps at least partly might explain these discrepancies is the fact that the object appears at random locations during automatic perimetry but in a more or less ordered sequence in manual perimetry Thus the patient is most often able to predict the position of the test object before it is seen and it might be tempting for him to change his fixation slightly when not observing the stimulus In fact, a close look at the patients fixation during manual perimetry reveals that fairly often, when a test object passes the border of a scotoma from a seeing to a non-seeing area fast, small eye movements in the direction of the dis appearing stimulus can be seen in the telescope" of the Goldmann perimeter As far as we know this phenomenon has not been explicitly described or analysed in the literature.

The aim of the present note is to demonstrate the existence of this phenomenon by the recording of eye movements during kinetic perimetry and also to show how the phenomenon is provoked or avoided in automatic perimetry

A Kinetic Perimetry

Material

Eleven patients with verified or suspected glaucoma were tested. Their ages ranged from 43 to 79 years (mean age 68 years) Patients who were very trained perimetric subjects were avoided as were patients known to cooperate badly in perimetry Nine pathological and two normal visual fields were examined. Some patients were chosen because their field defects had been missed by manual perimetry but detected by automatic perimetry

Only one eye was examined in each patient

Methods

Recording of eye movements Two disposable AgAgCl electrodes (Medicotest A 1o M) were used. They were placed lateral to the outer canthus of each eye A neutral electrode was placed above the left wrist The temple electrodes were connected to a small pre amplifier the output of which was fed to an ink recorder (Mingograf 24 B) The amplification of the recorder was so ad justed as to give a deviation of 10–20 mm in the ink written curve for a hori zontal eye movement of 30° A small marker switch was connected to the second channel of the recorder When pressed it produced markings on the ink written line of this channel

Control of perimeter stimulus The pantograph lever of the Goldmann perimeter was connected to a string driven by an electrical motor controlled from a drive

unit Through this arrangement the pantograph lever could be made to move along different straight lines on the visual field chart at even speed

Experiment

The patient was placed in the Goldmann perimeter and provided with correction for ametropia and near vision The electrodes were connected A filled in chart of the examined eye was put into the chart holder of the perimeter The stimulus was positioned at an eccentricity of about 35° The stimulus intensity was so adjusted as to be slightly supraliminal in this position The patient was instructed to keep his gaze steady at the fixation target of the perimeter and to signal if the stimulus disappeared The ink recorder and the movement of the stimulus were then started simultaneously and the stimulus travelled centripetally towards the fixation target of the perimeter at constant speed (usually 3°/sec) An assistant pressed the switch of the marker unit when the stimulus crossed the 30° circle and the fixation target At least two meridians were tested – each five times – in every subject One meridian crossed the blind spot or a known glaucomatous scotoma the other passed only through seeing areas The assistant was further instructed to press the button of the marker unit when any scotoma border was crossed The patient s fixation was constantly supervised in the telescope of the Goldmann perimeter

Results

Three patients demonstrated steady fixation in all tracings and one patient showed poor fixation in most tracings In the remaining seven patients there was a distinct difference in fixation when the stimulus passed through seeing and non seeing areas These patients usually maintained good fixation when the stimulus moved in seeing areas but when the stimulus passed into a scotoma they often obviously unconsciously changed their fixation in the direction of the stimulus recognized the stimulus and quickly resumed fixation again (Fig 1) Thus they never lost the stimulus and did not signal its disappearance These scotoma induced malfixations were not only recorded by the ink recorder but were also readily seen in the fixation monitoring telescope of the perimeter They were 7°–15° when the stimulus passed into the blind spot Thus the patients sometimes changed their fixation all the way to the test object but in some cases no more than to let the stimulus reach a seeing part of the visual field Four out of these seven patients never recognized the stimulus as missing and mostly demonstrated malfixation each time the stimulus entered a scotoma Three patients did not realize that the stimulus was missing in non seeing areas during the first trial but later found out that the stimulus

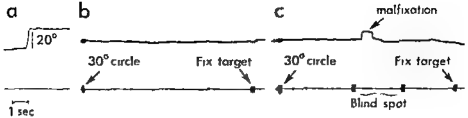

Fig 1

Recordings of eye movements (upper tracings) Markings (lower tracings)

a Calibration 20° horizontal eye movement
b Stimulus moving through seeing areas No eye movements occur
c Stimulus moving through blind spot Malfixation occurs when stimulus disappears into the blind spot area

disappeared When understanding this they showed proper fixation and signalled the disappearance of the stimulus In four of the patients circumscript pathological scotomata were tested in the other cases the blind spot was used Malfixations of the same type were elicited in both cases

B Automatic Perimetry

Material

Ten patients with verified or suspected glaucoma were tested Their ages ranged from 43 to 79 years (mean age 66 years) The same criteria for the selection of patients were used as described under Kinetic perimetry Seven of these patients were included in the material of Kinetic perimetry (see above) Left eyes were preferred because when using the non randomized logic described below the stimulus sequence is easier to predict in the blind spot area of the left than of the right eye (compare Fig 2)

Methods

An automatic perimeter described by Heijl & Krakau (1975b) was used It is a computer controlled perimeter with 64 static stimuli 56 of which are located at 5 10 and 15° of eccentricity The stimuli can be illuminated at 16 intensity levels the ratio between two consecutive levels is 1 2

Two different perimetric test logics were used

1 One test logic was identical to that used for glaucoma visual field screening (Heijl 1976) though the projected stimulus of the blind spot area was omitted.

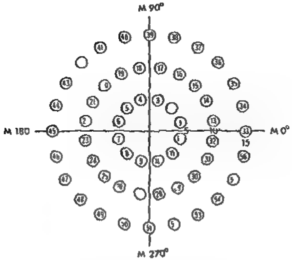

Fig 2

Test point pattern in the automatic perimetry Each test point is marked by a circle. In test logic 2 the stimuli are shown in ordered sequence beginning at point 1 and ending at point 56

The threshold was first determined by a repeated up and down staircase method at four points at 10° eccentricity The test point chosen among these four was decided by a random generator in the computer Using these thresholds the computer calculated supraliminal stimulus intensities to be used for the testing at the remaining 52 paracentral test points The testing in these points was then carried out with supraliminal stimuli During this testing the stimulus was exposed *at random* i e the position of the stimulus to be exposed was chosen by a random generator in the computer among the test points not yet ready tested

2 The second test logic used the thresholds obtained in the four points at 10 eccentricity with the first logic All 56 paracentral test points were then tested *in sequence* beginning at point 1 and ending at point 56 (Fig 2) The test points at 20° and 25 eccentricity were not used The test procedure at each point was identical to that in the first logic and the same intensity levels were used

Experiment

The patients were instructed to look steadily at the red fixation light of the perimeter during the whole test and to press the button whenever a stimulus was visible

The test were carried out at a background luminance of 1 0 or 0 1 cd/m All subjects were corrected for ametropia and for near vision The examination using the first test logic preceded the examination with the second test logic

Results

The measured threshold was zero (meaning no answer to the strongest intensity level of the perimeter) in a number of points in the field charts – denoting scotomatous areas In four patients there were very small differences between the results obtained by test logics 1 and 2 In the remaining six patients there was a difference of 1 to 6 in the number of points with threshold zero when the charts obtained with test logic 1 were compared to those of logic 2 and the field defects were smaller or even unrecognizable when the second (non randomized) logic was used (Compare Fig 3) In no case was the opposite tendency found

The correspondence between the results in the seven patients both in series A and B was satisfying In one of them the kinetic perimetry showed no mal fixation and there was no difference between automatic tests 1 and 2 in four there was malfixation in A and reduction of visual field defects in experiment B 2 In one case there was no malfixation in the recordings of eye movements

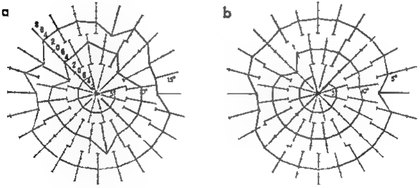

Fig 3
Pathological visual field

a Test logic 1 (randomized)
b Test logic 2 (non randomized)

Visual defects appears smaller with logic 2 than with logic 1 The measured threshold is zero in eleven test points in Fig a and in five test points in Fig b Intensity level numbers are marked along the 135° meridian of Fig a

but the non randomized logic showed reduction of scotomata compared with the randomized one the opposite malfixation but no reduction of scotoma size was found in one case Thus the frequencies of malfixation in A and of reduction of scotomata in B were similar

Discussion

The experiments with kinetic perimetry demonstrate that patients may exhibit a scotoma induced malfixation" i e they may change their fixation as soon as the stimulus enters a non seeing area although they maintain reliable fixation as long as the stimulus is seen This means that scotomata of blind spot size or even larger are easily missed at kinetic perimetry It might be pointed out that malfixation could also be elicited by switching off the stimulus but then the patients indicated the disappearance of the stimulus

The situation with a test object moving at a constant speed in kinetic perimetry has no exact counterpart in static perimetry The best approximation in our automatic perimeter may be to show the test points in ordered sequence along the three circles of test points (Fig 2) The experiments with automatic perimetry indicate that visual field defects are more often missed when static stimuli are presented in sequence i e at predictable places than when they are exposed in random order This is in agreement with earlier results obtained when comparing a randomized and a non randomized test logic for automatic perimetry (Heijl & Krakau 1975a)

The analogous results of the kinetic (A) and the automatic (B) test in the patients subjected to both support the assumption that the scotoma induced malfixation comes to the fore in both situations By randomization of the locations of consecutive stimuli such eye movements are largely prevented and this praxis permits us to detect visual field defects by automatic perimetry which have been overlooked in routine perimetry It also seems likely that the larger scotomata often recorded at automatic perimetry are nearer to the true size than those obtained at kinetic perimetry As for manual perimetry especially kinetic the importance of extremely careful monitoring of the patient s fixation during testing is evident

References

Armaly M F (1972) Selective perimetry for glaucomatous defects in ocular hypertension *Arch Ophthal (Chicago) 87* 518–524

Heijl A & Krakau C E T (1975a) An automatic static perimeter design and pilot study *Acta ophthal (Kbh) 53* 293–310

Heijl A & Krakau C E T (1975b) An automatic perimeter for glaucoma visual field screening and control Construction and clinical cases *Albrecht v Graefes Arch Ophthal 197* 13–23

Heijl A (1976) Automatic perimetry in glaucoma visual field screening A clinical study *Albrecht v Graefes Arch Ophthal 200* 21–37

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PSEUDODOUBLING OF THE OPTIC DISC

A Fluorescein Angiographic Study of a Case with Coloboma

BY

JAN KAARE BRINK and F ERLIN LARSEN

In a woman aged 45 with presbyopic complaints routine examination revealed pseudodoubling of the right optic disc and a colobomatous defect of the left eye The former was studied by fluorescein angiography
The differentiation between true doubling and pseudodoubling of the optic disc is discussed

Key words chorioretinal coloboma – pseudodoubling of the optic disc – fluorescein angiography

A doubling of the optic disc is an extremely rare phenomenon Only a few cases have been described Fluorescein angiographic examination has been reported in a single case only (Aouchiche et al 1971)

Below the result is stated of fluorescein angiography in a case where ophthalmoscopy revealed doubling of the right optic disc

Method

Fluorescein angiography was performed with a Topcon fundus camera after injection of 5 ml of 10 % sodium fluorescein into a cubital vein

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Case Report

A woman, aged 45 was subjected to routine examination owing to presbyopic complaints The patient's parents are not consanguineous, and her two children were found to have normal eyes

The visual acuity of her right eye was < [illegible] + 0.50 sph. -1.00 cyl. 90 Slit lamp examination disclosed a small central corneal maculation

Ophthalmoscopy (Fig 1) showed a normal optic disc with no cupping or pit formation The vessels ran normal courses to the upper quadrants The

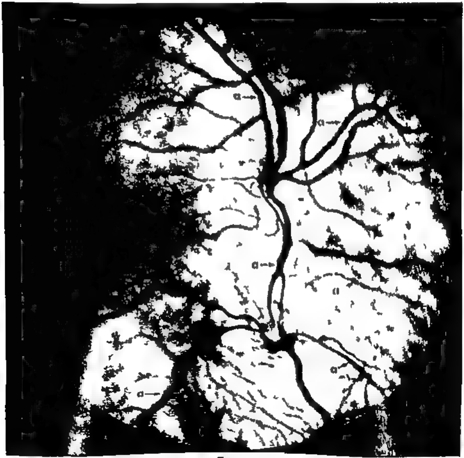

Fig 1

Right eye with normal optic disc and inferiorly the extra optic disc
a arteriole c choroidal arteriole

descending vessels were peculiar A large arteriole was seen to divide into two branches one disc diameter from the optic disc One further disc diameter distal to this the branches dived into an optic disc like lesion almost one disc diameter in size with central rounded cupping In this extra optic disc were seen another four fairly large vessels whose exact function could not be determined ophthalmoscopically The retinal pigmentation was scanty close to the extra optic disc and over a fanshaped area peripheral to this The macular area was normal

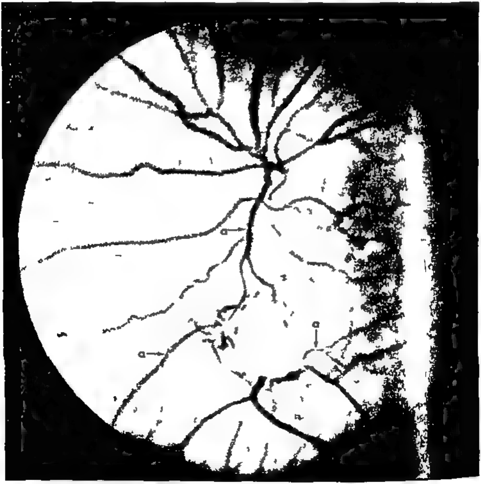

Fig 2
Left eye with normal optic disc and inferiorly a chorioretinal coloboma
a arteriole

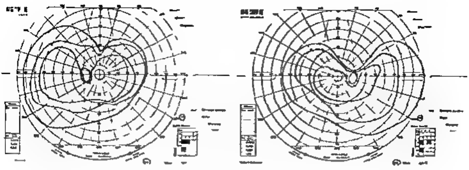

Fig 3
Goldmann perimetry showing nerve fibre defects in both eyes

The visual acuity of her left eye was 0 2 + 2 00 sph −2 00 cyl 5° Slit lamp examination disclosed a large tongue shaped corneal maculation there was no coloboma of the iris

Ophthalmoscopy (Fig 2) showed a normal optic disc The vessels to the upper retinal quadrants were normal whereas the descending vessels were peculiar A large arteriole was seen to descend and to give off two small rami nasally and temporally at the disc border Proper division of the arteriole occurred one disc diameter from the optic disc No venous drainage was found from the inferior retinal quadrants to the optic disc

1½ disc diameters below and immediately nasal to the described optic disc an atypical chorioretinal colobomatous region was seen about 1½ disc diameters in size with well defined cupping The lower temporal arteriolar branch was seen to pass across the coloboma being the only visible vessel within this region The venous drainage from the inferior quadrants on the other hand proceeded to the lower margins of the coloboma. Spots of hyperpigmentation could be seen along the edge of the coloboma The macular area was normal

Goldmann s perimetry showed typical nerve fibre defects in both eyes (Fig 3) X ray examination of the orbits concentrating especially on the optic foramina were normal

Results

Fluorescein angiography was performed to clarify the vascular conditions round the two optic discs in the right eye The results are technically somewhat un satisfactory due to the corneal maculation

Discussion

Typical colobomata of the retina and choroid occur between the time of invagination of the optic vesicle and the closure of the embryonic cleft i a between the 7th and 14th mm stage of development (4th to 5th week) (Duke Elder 1964 Mollenbach 1947) They are bilateral in 60 per cent of the cases and situated just below and slightly nasal to the optic disc Duke Elder writes as follows about atypical colobomata Colobomata associated with the prescence of abnormal vessels are rare and of two types either there is an abnormal anastomosis of retinal and choroidal vessels or a vessel issuing from the centre of the coloboma passing into the vitreous

On reviewing the literature concerning doubling of the optic disc it becomes evident that several different nosological entities must be considered Differentiation is difficult from chorioretinal coloboma and atrophy with secondary anastomosis of retinal and choroidal blood vessels whether due to vascular infectious or parasitic diseases

According to Duke Elder Elschnig in 1914 described a case of doubling of the optic nerve disclosed at autopsy Pesme (1948 1951) Rizzoli (1955) and Collier (1958) reported vessel communication between the optic disc and an extra disc whereas Trabut cited by Pesme (1948) and Kubik (1925) reported cases of double optic discs with independant vascular supplies Harmuth (1949) regarded his case of Schempapille" as a choroidal neurocele while Algan (1953) characterized his findings as a coloboma Alearts (1954) case of doubling of the optic disc is highly suggestive of an atypical coloboma of the optic nerve with epipapillary membrane and persistent hyaloid artery Campimetry revealed two distinct blind spots in cases mentioned by Collier (1958) and Rizzoli (1955) Lamba (1969) described bilateral coloboma of the choroid and doubling of the left optic disc together with presence of two optic foramina observed by X ray examination Aouchiche et al (1971) are the only writers who have given a fluorescein angiographic description of a patient in whom ophthalmoscopy raised suspicion of double optic disc Their angiography was performed and described by Amalric The suspected double optic disc was localized in the macular region and the fluorescein angiography suggested a chorioretinal cicatrix rather than a doubling of the optic disc Amalric stated that ciliary arterioles may replace branches from the central retinal artery and that the appearance of such a ciliary arteriole on the retina may create an illusion of an extra optic disc Finally Amalric claims that anastomoses of choroidal and retinal vessels may be seen in parasitic and inflammatory diseases Ehlers (1953) mentioned as another differential diagnostic possibility that patients with proliferative diabetic retinopathy may show invasion of choroidal vessels at a retinal level with

consequent appearance of multiple pseudo discs Elbrechtz (1975) described a pseudo disc situated above the normal disc with numerous anastomosis of vessels between the two discs

Our patient had a chorioretinal coloboma of the left eye and the defects of the right were likewise of the colobomatous type but with an abnormal supply of vessels The delayed cilioretinal arteriolar filling of the upper disc suggests as much We cannot say for certain whether the delayed arteriolar filling of the extra disc is due to a delayed cilioretinal arteriolar filling or to a partial constriction of the arteriole coming from the upper disc Finally our patient presented typical nerve fibre defects which were in principle similar in both eyes

The finding of a double optic disc should only be characterized as true doubling if the following requirements are fulfilled

The extra optic disc must be supplied with nerve fibres demonstrable on interference filter takings and by perimetry The optic discs must have separate vascular supplies or at least a communicated arterial supply from the primary optic disc demonstrated by fluorescein angiography Further computerassisted axial tomography (EMI scanning) must disclose two optic nerves leaving the eyeball and X ray examination possibly two optic foramina

Acknowledgments

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References

Alaerts M L (1954) Un cas de dedoublement du nerf optique et de l artere centrale de la retine *Bull Soc belge Ophtal 108* 574–575

Algan M B (1953) Aspect ophthalmoscopique de pap lle surnumeraire *Bull Soc Ophtal France* 147–148

Aouchiche M Boyer R & Zetchi A (1971) A propos du diagnostic des doubles papilles *Bull Soc franç Ophtal 84* 695–635

Collier M (1958) Les doubles papilles optiques *Bull Soc franç Ophtal 71* 328–332

Duke Elder S & Cook C (1964) *System of Ophthalmology* Vol III part 2 Normal and abnormal development Henry Kimpton London

Ehlers H (1953) Ophthalmoscopical findings in proliferative diabetic retinopathy *Acta ophthal (Kbh) 31* 289–297

Elbrechtz H C (1975) Über eine doppelte Papille im Auge *Klin Mbl Augenheilk 166* 289–391

Harmuth E (1949) Über das ophthalmoskopische Bild einer Neurocele chorioidalis bei kongenitalem Kolobom der Aderhaut *Klin Mbl Augenheilk 115* 351–354

Kubik A (1925) Abnorme Opticusteilung *Klin Mbl Augenheilk 75* 775

Lamba P A (1969) Doubling of the Papilla *Acta ophthal (Kbh) 47* 4–9

Møllenbach C J (1947) *Medfødte defekter i øjets indre hinder* Nyt Nordisk Forlag - Arnold Busck København 1947

Pesme P (1948) Double papille optique d un seul cote *Bull Soc franç Ophtal 61* 323–327

Pesme P (1951) Un nouveau cas de papille double *Bull Soc Ophtal France* 867–868

Rizzoli E (1955) Contributo alla conescenza delle anomalie congenite del nervo ottico un caso di duplicita papillare. *Rass ital Ottal 24* 357–362

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TRANSACTIONS OF THE SWEDISH OPHTHALMOLOGICAL SOCIETY 1976

EDITED BY

GUNNAR LENNERSTRAND

Meeting in Gothenburg June 11 1976
Symposium on Disc Swelling and Optic Atrophy

J Sjostrand *The anatomy and physiology of the optic disc*

Anatomy and histology The intraocular portion of the optic nerve or the optic nerve head can be subdivided into retinal choroidal and scleral parts The portion of the optic nerve head visualized ophthalmoscopically is called the optic disc

The axons and neuroglial cells of the optic nerve head are of neuroectodermal origin Not infrequently remnants of glial cells are left in adult life in front of the optic disc and can be observed as epipapillary membranes These membranes are of clinical importance since they can hide pathological changes occurring in the optic disc behind them

The optic nerve head consists of bundles of axons and of columns of spider shaped astrocytes In the lamina cribrosa the axons pass through the fenestrations of the collagen sheets The morphological features of the lamina cribrosa are emphasized since the possibility exists that already a slight misalignment of the fenestrations due to changes in intraocular pressure may cause a strangulation of the axons

Circulation and vascular anatomy The optic nerve head has a complex circulation In this region three arterial and two venous systems meet and it is of clinical importance that the circulation is influenced by the intraocular and the intra cranial pressure The capillaries of the optic nerve head have no fenestrations and tight junctions join the endothelial cells The capillaries are impermeable to fluorescein and a blood optic nerve barrier exists Some leakage of material however occurs from the surrounding choroid

The nerve fibres of the optic nerve head About 1 million axons pass through the optic nerve head This region has been studied intensively in experimental work to elucidate the pathophysiology of nerve fibre atrophy in ocular disease Besides the

current hypothesis of ischemic tissue damage as the cause of axon degeneration it has been suggested recently that mechanical factors at the level of the lamina cribrosa play an important role

L Frisen *Normal and anomalous optic discs*

H Bynke *Optic disc oedema in intracranial and arterial hypertension optic neuritis and ischaemic optic neuropathy*

M Lundstrom *Descending optic atrophy*

Meeting in Jonkoping September 11–12 1976
Symposium on Amblyopia Early Recognition and Treatment

Moderator *E Gregersen*

E Gregersen *Amblyopia Introduction*

An account is given of present views on squint amblyopia and anisometropic amblyopia as modified deprivation amblyopia i e amblyopia that may be attributed to deprivation of focusing foveal stimuli

Differences from and similarities to total deprivation amblyopia (e g in dense congenital cataract) are emphasised and the electrophysiological and histological changes in amblyopia are described

E Diderholm *Ophthalmological findings at regular check ups in 4 year olds*

Material

Of 3547 four years olds born in the country of Uppsala in 1969 3441 (97 %) attended the regular check up of four year olds at the children s clinic

545 children (16 %) were referred due to a visual acuity of less than 1 0 in the poorer eye when tested with single Snellens E and/or suspected or confirmed strabismus or other eye complaint not already under specialist care

509 of the 545 referred patients kept their appointment with the ophthalmologist 479 chosen at random were examined by myself and are accounted for here

Methods

Ophthalmic examination of all the children consisted of Javal Wirt Fly Test plus ABC cover test for near and distance ocular movements convergence visual acuity without optical correction tested with Snellens E in rows Regardless of the visual acuity a cyclogyl® refraction was performed If the visual acuity was 0 6 or less in the poor eye and/or the difference in the visual acuity between the right and left eye $\geq$ 2/10 (2 lines) then depending upon the result of objective refraction and the child s co operation a subjective refraction was carried out at a later date and any possible optical correction and/or occlusion treatment was initiated

Results

3 diagnoses dominated ametropia anisometropia with amblyopia and strabismus
With regard to the refractive error of the poorer eye the following was found –
21 patients had hypermetropia ≥ 4 D (9 patients ≥ 6 D)
14 had myopia ≥ 2 D (10 patients ≥ 3 D)
74 had astigmatism ≥ 2 D (23 patients ≥ 3 D)

totaling 109 patients with significant refractive errors (anisometropia not included) 78 of the patients received their refractive correction immediately a further 39 developed better visual acuity ($\geq$ 9/10 [2 lines]) without receiving their correction immediately

Anisometropia with amblyopia but without strabismus (difference in VA between right and left eye $\geq$ 2/10 with glasses) was diagnosed in 21 cases and occlusion therapy initiated

49 squints were discovered 22 had amblyopia and were given occlusion treatment 28 of the squints were convergent 21 with amblyopia 12 of the convergent squints were microstrabismus 11 of which had amblyopia 12 were permanent large angle squints 10 with amblyopia 4 were intermittent squints without amblyopia

19 were divergent squints the majority intermittent and only one with amblyopia was found

1 Duane's refraction syndrome 1 overaction of the inferior oblique both of which were not amblyopic were diagnosed

Apart from these one or two cases of nystagmus blepharitis eyelid eczema anisochoria also previous history of perforation and retinochoroiditis

Table I

Newly detected significant eye disorders in 7 year old children with and without eye screening at 4 years of age

	Newly detected significant eye disorder		No newly detected significant eye disorder		Sum	
	n	%	n	%	n	%
Previously eye screened at 4 years of age with normal result	11	0.7	1519	99.3	1530	100
Previously not eye screened	29	4.5	619	95.5	648	100
Sum	40	1.8	2138	98.2	2178	100

Summary

Of the 429 patients examined 50 % were free from ophthalmic complaints In 18 % treatment could have waited until the next check up at the age of 7 years 32 % were in need of treatment before starting school in their seventh year

G Stigmar & L Kohler *A follow up of a preschool vision screening program*

In 2178 seven year old children vision screening was performed at school by nurses using Snellen E charts 310 children (14 2 %) with visual acuity of 0 9 or below were referred for further ophthalmological evaluation

In addition to the conventional presentation of the results based on visual acuity refraction and eye position an attempt has been made to evaluate the ophthalmological findings according to the importance for the children s health the prognosis and the need for professional care 7 2 % of all children screened showed either no or only insignificant abnormalities at the ophthalmological examination The children with significant eye disorders constituted 7 0 %

The most important information about the value of the preschool screening test is shown in Table I Significant eye disorders were detected considerably more often in those children who had not been examined at 4 years of age (4.5 % vs 0 7 %) Expressed in another way without the screening at 4 years of age 40 instead of 11 children in our material would have had eye disorders necessitating treatment.

Thus it can be concluded that vision screening of 4 year old children is of great importance and should be included in the regular child health services

A Hedin *Testing visual acuity in children*

To be published in Augenarztliche Fortbildung

G Lennerstrand *Recent advances in extraocular muscle physiology*

E Gregersen J Pontoppidan & E Rindziunski *Atropine resistant residual accommodation*

Among 25 children with squint amblyopia who had been receiving atropine 1 % daily in the dominant eye for an average of 10 months four showed spontaneous atropine resistant residual accommodation (a r r a) in the atropine treated eye The a r r a occurred in a permanent transient or intermittent form and ranged from 2–15 D

The occurrence of spontaneous a r r a in the present small series indicates (1) That in several cases atropine cycloplegia represents merely a cycloparesis not a cyclo paralysis i e that retinoscopy can hardly be interpreted as a constant value in all patients (2) That penalisation therapy will fail in the event of permanent a r r a (3) That a finding of increased hypermetropia at repeated retinoscopy seems to bear no relation to the spontaneous a r r a which appears to represent dynamic refraction i e accommodation and not static refraction

G Aurell *Results of penalisation cases*

The purpose of the investigation was to gain an opinion of the value of near penalisation (PE) in cases of amblyopia in squint especially with regard to an improve ment of visual acuity and the detection of a latent hyperopia and the possibility of

reducing the strabismus angle Groups of between 122 and 137 children aged 2–10 years were treated The periods of treatment varied from 6 to 30 months but generally lasted 12–18 months

Visual acuity With the treatment mentioned above a considerable visual improvement was obtained in some 50 per cent of the cases independent of whether or not the PE was commenced at an early stage or later on and of whether or not the children had previously been treated with occlusion without any positive result The exceptions were those whose squint had started *early* (discovered at latest when the child was one year of age) The amount of improvement in these cases was only 30 per cent and the visual acuity improvement was very small on an average 2/10 versus 4/10 for the others

In cases of *eccentric fixation* we succeeded in gaining a considerable visual improvement in 3 cases out of 12 All cases had previously been treated with occlusion without any result

Change of refraction (122 cases) In near penalisation the better eye was treated with atropine and the amblyopic eye was over corrected by 2–3 5 dptr During the treatment the objectively measured refraction was increased by 0 5 to 2 5 dptr in 50 per cent of the cases (the average was 1 dptr) An increase of refraction was also obtained in the other eye In these cases the increase was about 0 5 dptr less than in the atropinized eye In 7 cases the refraction *decreased* by approx 1 dptr

The angle of squint (124 cases) was reduced during the treatment in 65 per cent of the cases (2–15° average 6°) Owing to these results some operations could be completely omitted and in many accomodative cases we could avoid the frequent re operations Some of the angle reductions were of course results of a more complete correction of the hyperopia made possible by the penalisation s evocation of the latent hyperopia

Symposium on Visual Demands in Road Traffic

Moderator *G von Bahr*

K Rumar *Vision in traffic*

Even if driving is mainly based on visual information experience from e g driving simulators tells us that other information channels are also important The information presented to the visual system is enormous and has to be selected This is carried out higher up in our nervous system Some aspects of this selection can be studied by means of registration of drivers eye movements

The functions normally used to characterize vision are of course also important in traffic *Contrast sensitivity* is decisive for detection at low levels of illumination *Visual acuity* is important for understanding and judgement at long distances Night myopia is a special problem which it is possible to correct The *visual field* is especially important in urban traffic where detection of other road users often occurs with peripheral vision Binocular *three dimensional vision* is probably only used at very short distances such as in parking *Colour vision* has some relevance for detection of signs and vehicles and for perception of signals *Accommodation* may be crucial by

changing fixation between traffic and instruments and by used of convex rear view mirrors

To summarize man s visual performance is limited the possibility of eliminating these limitations by training is minimal Therefore correction of visual deficiencies is important But in the long run the only rational strategy is to try to adapt traffic environment to man s visual characteristics

A Hedin *Subnormal traffic vision*

The major part of a driver s information input is visual However the relative significance of the various visual functions is not known and clear cut requirements for drivers cannot be established It should be emphasized that familiarity with a driver s *vision* is more important than information on the presence or absence of specific eye diseases

The most valid vision test for drivers – extended periods of driving in traffic – cannot be used for practical reasons In a simulator all possible risk situations cannot be tested Accordingly practical experience and educated guesses have led to the selection of certain visual functions to be tested and to a definition of the normal limits of these tests Many studies have tried to correlate visual aptitude and traffic behaviour Inherent difficulties and systematic errors have diminished the value of many of these studies A correlation has however been shown to exist between certain visual abilities and the number of traffic violations or accidents but it has as yet not been possible to define norms for these visual functions

Among the visual functions tested today are static visual acuity visual field eye movements and colour vision Limits to the degree of ametropia are laid down mainly on the basis of the peripheral prismatic effect of strong lenses Subnormal stereo vision lateral phoria and squint do not influence normal driving while any form of double vision disqualifies from driving In the future dynamic visual acuity might replace static acuity because the former is better correlated to traffic behaviour The thresholds of angular subtense and movement may also be incorporated in a battery of traffic vision tests It is hoped that the crucial problem of night driving will also be taken into account i e that driving applicants are tested as to their acuity in low luminances their glare sensitivity and readaptation after glare

G von Bahr *Recommendations for the issuing for certificates*

Meeting in Stockholm December 2–3 1976
General Session

A Heijl *Automatic perimetry for glaucoma screening*

A large number of the patients who are being checked in the glaucoma departments of this country have not yet developed any documented visual field defects The primary goal of perimetry in these cases is to find out whether glaucomatous visual field defects do exist or not Fully automatic computerized perimetry was used for visual field screening in 181 eyes of 100 patients from a glaucoma out patient de partment

Methods A computerized fully automatic perimeter with 64 static stimuli according to Heijl and Krakau was used The stimuli are concentrated in the paracentral area and can be regulated over 16 intensity levels The testing procedure the glaucoma screening test logic is programmed in a mini computer The patient answers to perceived stimuli by pushing a button and all the time his answers influence the remaining part of the test Usually the test time is somewhat less than 4 minutes per eye The test result is presented on a teletype and is plotted as static profiles in a polar co ordinate system by a graphic plotter

As a method of comparison Armaly s selective perimetry was used in a slightly modified form Control methods were static profile perimetry and kinetic perimetry

Results 47 pathological visual fields were discovered All were identified by the automatic perimeter while one was missed by the manual selective perimetry The false positives were 15 5 % in the automatic perimetry 11 % in the manual (on condition that a second presentation of initially missed paracentral points was allowed in the manual selective perimetry) By a second screening the number of false positives could be greatly reduced to 3 9 % or 3 3 % respectively

A very remarkable fact was that 20 of the 47 pathological fields had been classified as normal at the previous check up The fact that so many more field defects were detected in this study might be explained by the very favourable conditions under which our perimetrist was working – conditions which are almost impossible to establish in conventional clinical work

Conclusion Fully automatic computerized perimetry can be as effective as Armaly s selective perimetry when the latter is used by a trained perimetrist, who is allowed to work under optimal conditions The automatic perimetry is superior to clinical routine perimetry

Reference Heijl A (1976) Automatic perimetry in glaucoma visual field screening A clincal study Graefes Archiv *200* 21–37

O Pallin K G Brege & K M Lundmark *Interferon in servere herpes simplex of cornea*

(Published in Lancet May 29 1976 p 1187)

D Epstein & B Philipson *Complications associated with the wearing of contact lenses*

Contact lenses are gaining ground in Sweden but their popularity exceeds the physician s as well as the public s knowledge of potential hazards associated with their use.

In a four month survey conducted at the Department of Ophthalmology Karolinska sjukhuset Stockholm a total of 36 instances of complications secondary to contact lens wear were registered

The majority of the patients involved wore soft lenses Corneal lesions were found found in most cases

Two of the patients required hospitalization because of corneal ulcerations Several others suffered discomfort for a good number of weeks No gross irreversible lesions with permanent loss of vision were noted

This survey represents a timely reminder that the wearing of contact lenses is an abnormal condition which can result in serious complications

There is an obvious need for a more rigorous and systematic control of contact lens wearers by the ophthalmologist This in turn requires better cooperation between physician and optician

However the ophthalmologist s training in this rapidly expanding field must also improve if he is to have a reasonable chance at reducing the number of complications

E Wold *Eine neue Methode ur Befestigung des Plastikrohrchens bei der Tranenrohrchenrekonstruktion nach Worst*

Bei der operativen Tranenrohrchenversorgung nach Worst wird ein Plastikrohrchen mit Hilfe des Figtail instrumentes eingefuhrt und die beiden Enden des Rohrchens werden in der Lidspalte zusammengenaht Nach unserer Erfahrung scheuern diese dann gegen den Augapfel und Hornhauterosionen und entzundungen entstehen die oft das Entfernen des Plastikrohrchens notwendig machen bevor die Heilung des Tranenrohrchens erfolgt ist

Die Knickung des Plastikrohrchens mit einer aufgewarmten Pinzette ist eine besseres Befestigungsverfahren Fur die Aufwarmung der Pinzette haben wir eine einfachen Apparat konstruiert der aus einem Lotkolbenelement (100 Watt) besteht dessen Kupferspitze durch einen Aluminiumstab ersetzt worden ist Die Temperatur wird durch einen Thermostat geregelt (Bei dem Plastikrohrchen von Medical Workshop das wir verwendet haben werden 150–160°C benotigt um einen bestehenden Knick herbeizufuhren Bei 180°C schmilzt das Rohrchen) Die Pinzette wird in ein Loch im Aluminiumstab gesetzt und gewarmt Mit der warmen Pinzette werden die Plastikrohrchen an den Tranenpunktchen senkrecht vom Augapfel weggeknickt und ein bis zwei mm weiter distal nochmal zur Nasenwurzel hin geknickt Die Enden werden auf einen cm Lange gekurzt und mit einem Thermokauter zusammengeschmolzen Wenn die posttraumatische Schwellung zuruckgegangen ist muss man eventuell den Knick korrigieren damit das Plastikrohrchen den Augapfel nicht beruhrt

Wir haben in Örebro und Borås von 1970–1975 einundzwanzig Patienten mit verletzten unteren Tranenrohrchen nach dieser Methode operiert Als einzige Komplikation haben wir in ein paar Fallen ein leichtes Aufschlitzen des Tranenpunktchens gesehen Die Durchgangigkeit des Tranenrohrchens war bei unseren Fallen am besten wenn das Plastikrohrchen 4–6 Monate im Gangsystem behalten wurde

Bei der operativen Versorgung verletzter Tranenrohrchen ist eine richtig ausgefuhrte Warmeknickung des Plastikrohrchens eine einfache und gute Methode zur Befestigung desselben Der Patient kann beschwerdefrei das Plastikrohrchen im Gangsystem behalten bis Heilung eingetreten und die Strikturgefahr nicht mehr so gross ist

P Algvere & B Rosengren *Ocular immobilization in the treatment of retinal detachment*

Sixty five non selected eyes with primary rhegmatogenous retinal detachment were immobilized by traction sutures usually under m rectus inferior and medialis respectively The immobilization was used in most eyes for 2–3 days (range 1–5 days) prior to surgery An almost complete spontaneous reattachment occurred in 45 % of the cases a partial reattachment (i e more than half of the detached area) was seen in 37 % but no reattachment took place in 18 % This rate of spontaneous reattach

ment is significantly higher than that obtained by bilateral eye patching and complete bed rest

Postoperatively the eye was immobilized by one traction suture under the inferior rectus muscle usually for 3–5 days (range 3–7 days) No patient was confined to bed

The rapid saccadic eye movements that are eliminated by ocular immobilization are considered to be one crucial factor counteracting retinal reattachment Eyes in which preoperative reattachment is achieved can be cured by simple surgical procedures and have a favourable prognosis

C J Linde D Epstein B Jerndal & P Algvere *Ocular diagnosis with B scan ultrasonography*

A Coleman Ophthalmoscan with a simultaneous recording of both A scan and B scan has now been in use at the Department of Ophthalmology Karolinska sjukhuset Stockholm for the past several months Some 60 eyes have been examined to date These included retinal detachment choroidal effusion choroidal neoplasm/metastasis and vitreous hemorrhage (traumatic diabetic)

A funnel shaped total retinal detachment is easily recognized with the aid of a *B scan It can be readily distinguished from the membranes seen at the posterior border* of a detached vitreous following vitreous hemorrhage The fact that this distinction can be made means that crucial information can be obtained prior to the selection of eyes for pars plana vitrectomy

However difficulties may be encountered when attempts are made to distinguish preretinal vitreous membranes in the posterior pole (as in proliferative diabetic retinopathy) from a flat retinal detachment A very valuable diagnostic sign seen in malignant melanoma of the choroid is the acoustic shadow obtained when frequencies of 15 or 20 MHz are used

These examples illustrate that the B scan is an indispensable diagnostic tool when analyzing eyes with opaque media

O Textorius K O Skoog & S E G Nilsson *The relationship between the stimulus duration and the amplitude of the human d c registered c wave*

The aim of the present study was to analyse in detail the dependence of the human c wave on stimulus duration with special reference to the influence of different superimposed off responses

Method Six healthy volunteers participated in the investigation The c wave was studied at different stimulus durations (from 0 13 to [illegible] s) with d c technique which permitted stable and reproducible recordings

Results and conclusion With increasing stimulus lengths the implicit time of the c wave (measured from on to c wave peak) increased up to a maximum of about 5 5 s Also the amplitude of the c wave rose to a plateau which was reached after 4 s stimulus duration However the amplitude was influenced by positive and negative slow off effects seen in most volunteers and at several stimulus lengths superimposed upon the peak of the c wave This fact must be considered when developing a standardized method *for measuring the c wave amplitude proper*

Ilmari Rendahl Lecture

C. H. Dohlman: *Recent advances in the treatment of corneal disorders*

Symposium on Recent Advances in Treatment of Corneal Disorders

Moderator: *C. H. Dohlman*

Participants: *M. Norn, B. Hedbys, A. Anseth*

Pierre Francois and Mireille Bonnet La macula Paris 1976 Masson p 487 37 coloured plates and 389 illustrations

This is another valuable book in the series of ophthalmological monographs published under the aegis of la Societe Francaise d Ophtalmologie The principal authors are Pierre Francois from Lille and Mireille Bonnet from Lyon

The first part of the book consists of a description of the normal anatomy and physiology of the macula together with the functional and physical methods of examination (ophthalmoscopy biomicroscopy retinography and angiography) The importance of the simple and important biomicroscopical examination technique by means of the contact lens is especially stressed

The second part of the book describes the pathological macula To begin with a general description of the symptoms and signs of macula disease with their clinical manifestations (oedema exudates haemorrhages atrophy and retinal folds) is given This is followed by a section on macula diseases which comprises the most important part of the book The diseases of the macula are divided into groups in which each individual disease is described in a clear and comprehensive fashion (clinical photographs angiography treatment etc) This makes the book much easier to use for reference purposes

The book is richly illustrated with diagrams histological photographs black and white retinograms and angiograms and 37 plates largely comprising coloured retinal photographs with 2–8 per plate The coloured retinograms are of excellent quality as are the remaining black and white illustrations The fluorescein angiograms are of especially high quality

The discussion concerning the forms of treatment for macula diseases including photocoagulation is characterised by the authors considerable experience in this field Their advice on this matter is realistic and down to earth

Each section is accompanied by adequate references to the literature

The book is an excellent example of the high standard of French ophthalmology and is indispensable for anyone concerned with macula diseases

S E Lorent en

Hu h O Barber and Charles W Stockwell Manual of Electronystagmography The C V Mosby Company St Louis Missouri 63103 1976 20 pages 396 illustrations Price US dollars 25 /5

It is evident from the preface that with their book on electronystagmography (ENG) the authors not only aim at informing the reader about the principles of electronystagmography but also give practical advice about the design and organisation of an ENG laboratory The book is intended for both the doctor who wishes to incorporate the ENG in his examination routine as well as for the technician or nurse who is in charge of the daily examination procedure Consequently the first chapters comprise an introduction to the recording of eye movements by the ENG the basic principles for the ENG and the various types of eye movements and their control via the oculo

motor nerve from the premotor and motor areas The functions of the saccade control system and the pursuit control system are also described with regard to the consequences of lesions in these systems The vestibularly control system as well as the anatomy and physiology of the labyrinth are described in a clear and simple fashion with easily understandable illustrations

In chapter 3 the authors give detailed descriptions of the organisation of an ENG laboratory with electrical installations tables and chairs etc and considerable attention is naturally paid to the actual apparatus used for registering electrodes nystagmograph the vestibulary and visual stimulators

Chapter 4 deals with the preparations for the testing and this chapter also contains a rather short but otherwise excellent survey of the most frequently found artefacts with ENG

At the beginning of the book the authors recommend six tests for the electronystagmographic examination of the oculomotory and vestibulary systems The practical arrangement of these tests is dealt with in chapter 3 while chapters 5 6 7 and 8 describe the electronystagmographic findings with the various tests i e gaze test saccade tracking and optokinetic test positional test and Hallpike manoeuvre as well as the caloric test For each test there is a short description of the normal electronystagmogram including the variations found within the normal limits Following this a series of pathological nystagmograms with the underlying lesions is described Also the possible sources of error are examined e g abnormal eye movements after the taking of medicaments In chapter 9 it is shown how to register and draw conclusions from the electronystagmographic findings

At the end of the book there are 17 pages with questions and answers – with a series of abnormal ENG tracings which the readers should attempt to interpret On the final pages there is a literature list as well as the answers to the questions posed

The book is a reference manual on electronystagmography and as such is excellent It is easy to read and easy to understand even for the person who has not previously been concerned with this sub peciality It should therefore be found in any ENG laboratory

Svend Faurschou Jensen

VARIA

Second International Symposium on Immunology and Immuno pathology of the Eye

In association with the XXIII International Congress of Ophthalmology the Second International Symposium on Immunology and Immunopathology of the Eye will be held in San Francisco California on May 8–10 1978

The tentative program includes sessions on Immunopathology of Uveitis Tumor Immunology Herpetic Keratouveitis Immunogenetics Corneal Transplantation and General Ocular Immunology

For further information contact Arthur M Silverstein Ph D The Wilmer Institute Johns Hopkins Hospital Baltimore Maryland 21205 USA

The XIth Hellenic Congress of Ophthalmology

will take place in Chalkidiki (Kassandra penisula) from June 15 to 18 1978
Subject Tumors of the eyeball
Simultaneous translation in Greek English French and German language
Address 11th Hellenic Congress of Ophthalmology
P O Box 497 – Thessaloniki Greece

European Ophthalmic Pathology Society

The European Ophthalmic Pathology Society held its 16th Annual Meeting in Munich Germany June 14th–17th 1977
The meeting was scientifically and socially of an exceptionally high standard and was excellently organized by Professor O E Lund and Mrs Lund
Dr W R Green (Baltimore) was the honoured guest
Professor J Bock (Austria) and Dr P Dhermy (France) were unable to attend
Professor Bock resigned and two new members were elected – Dr E Balestrazzi (Italy) and Dr F Stefani (Germany)
The next meeting of the Society will be held in Belgrade Yugoslavia with Professor Olga Litricin as Organizing Secretary

S Ry Andersen

3rd International Visual Field Symposium

The International Perimetric Society (IPS) announces The 3rd International Visual Field Symposium in Tokyo Japan (3–6 May 1978)
Open to all IPS members and their guests
For all information contact Dr E L Greve Eye Clinic University of Amsterdam Wilhelmina Gasthuis Eerste Helmerstraat 104 Amsterdam 1018 The Netherlands

Correction

Acta ophthal (Kbh) Suppl 130 1977 *Studies on the Mechanism of the Breakdown of the Blood Aqueous Barrier in the Rabbit Eye* by Elisabeth Bengtsson

The sentence on page 26 line 11 from the top beginning with The flare response to PGE_1 should be as follows

The flare response to arachidonic acid (AA) but not to PGE could be inhibited by indomethacin which is known to inhibit the conversion of AA to GE

*Division of Ophthalmology**
(Head A R Rosenthal)
*and the Division of Diagnostic Radiology **
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COMPUTERIZED TOMOGRAPHY OF THE ORBITS

A Report of 196 Patients

BY

E NIKOSKELAINEN [1] D R ENZMANN** E L SOGG and
A R ROSENTHAL

The value of orbital CCT scans was studied by grouping the CCT scans of 196 patients into clinical diagnostic categories In 83 % of patients with suspected Graves ophthalmopathy CCT confirmed the diagnosis The CCT scan differentiated patients with Graves' disease from those with orbital pseudotumour or malignancies The CCT scan was positive in 92 % of patients with proven orbital malignancies In 73 % of patients with proptosis of unknown aetiology and in 56 % of patients with ocular motility problems the CCT scan led to the diagnosis The CCT scan ruled out orbital mass lesions in cases of optic neuritis optic atrophy or vascular malformations The greatest value of the CCT scan was in the localization and determination of the size and shape of various orbital lesions and in the accurate follow up of those lesions utilizing serial scans

Key words computerized tomography – cranial computed tomography – Graves disease – orbital pseudotumour – EMI scanner – orbital malignancy – proptosis – exophthalmos – thyroid ophthalmopathy

The cranial computed tomographic (CCT) scan is a new non invasive and accurate modality in the investigation of orbital pathology (Alper et al 1975 Ambrose et al 1974 Baker et al 1974 Dallow et al 1976 Gawler et al 1974

[1] Dr Nikoskelainen was a Postdoctoral Fellow in Clinical Neuro ophthalmology and is now with the Department of Ophthalmology The University Central Hospital of Turku Turku Finland

Received March 29 1977

Grove et al 1975 Hilal et al 1976 Jakobs & Kinkel 1976 Lampert et al 1974 Leone & Wilson 1976 Momose et al 1975 Weinstein et al 1976 Wright et al 1975) Some disease processes such as Graves disease and orbital pseudotumour may demonstrate characteristic CCT scan abnormalities (Enzmann et al 1976a b) but many orbital CCT scan findings are non specific The detection rate of the CCT scan for orbital pathology is high but not all orbital abnormalities are equally well displayed The present study compares the findings on the CCT scan with the initial clinical diagnosis and the final diagnosis to demonstrate the utility of this technique in various clinical settings The diagnosis missed by CCT scanning may be due to failure of the scan to detect the lesion failure in interpretation of the scan or failure to obtain a complete scan

Patients and Methods

Of the first 5300 CCT scan examinations performed with the EMI scanner (Electrical and Musical Industries Ltd) at Stanford University Medical Center orbital scans of 218 patients were analyzed Technically inadequate scans (5) and old 80 x 80 matrix scans (17) were not analyzed further Thus 196 patients were studied of which 39 had serial scans The patients were referred for signs and symptoms suggesting an orbital problem the most common complaints being proptosis diplopia and decreased vision Clinical data and the final diagnosis were obtained from review of hospital records or from referring physicians The follow up period of the patients varied from five months to two years

CCT scans were performed at 0 degrees to Reids base line (orbitomeatal line) with a separated 5 mm collimator system and the 160 x 160 matrix (Enzmann et al 1976a b Hayward & Zatz 1975) In order to increase the visibility of lesions contrast medium infusion (4 4 ml/kg methylglucamine diatrizoate [Hypaque®] 30 % Sterling Winthrop) was utilized routinely in all patients except in some with Graves disease A complete examination required visualization of the inferior mid and superior orbit and the frontal and maxillary sinuses

Results

The 196 patients were grouped according to the initial clinical impression (Table I) and then analyzed in view of the CCT scan findings and the final diagnosis

Table I

Clinical diagnosis before CCT scan in 196 patients

	No of patients	Per cent
Graves disease	78	39 8
Known malignant disease with question of orbital involvement	46	23 5
Unknown unilateral proptosis	2[illegible]	11 2
Eye motility problem of unknown aetiology	9	4 6
Decreased vision and/or visual field defect of unknown aetiology	10	5 1
Optic neuritis	8	4 1
Optic atrophy	4	2 0
Miscellaneous	19	9[illegible]
Total	196	100 0

Table II

CCT scan finding in 78 patients with initial diagnosis of Graves disease

Clinical diagnosis	CCT scan characteristic of Graves disease	CCT scan normal	CCT scan other diagnosis than Graves disease	Total
Suspected Graves disease with ophthalmopathy	59	10	4*	73
Suspected Graves disease without ophthalmopathy	2	3	0	[illegible]
Total	[illegible]	13	4	78

* pseudotumour 3 metastasis of breast carcinoma 1

Fig 1

Sixty two year old female with severe Graves ophthalmopathy CCT scans show the characteristic bilateral symmetric extraocular muscle enlargement The inferior (arrow A) medial (white arrow B) lateral (open arrow B C) and superior rectus muscles (arrow D) all are bilaterally enlarged Optic nerves are of normal size

Graves disease Of the 78 patients thought to have Graves disease 74 proved to have it but in four patients the CCT scan revealed the initial diagnosis to be incorrect (Table II) The typical findings in Graves disease symmetrically enlarged extraocular muscles involving primarily the medial inferior and lateral rectus muscles were found in 61 of these 74 patients (Fig 1) In the remaining 13 patients who had minimal ophthalmopathy the CCT scan was normal and excluded other mass lesions In addition to the patients with initial diagnosis of Graves disease three patients with unilateral proptosis and one with an eye motility problem were shown to have Graves disease on the CCT scan The CCT scan demonstrated the characteristic CCT scan findings in 65 (83 %) out of the 78 total patients with Graves disease In four of (patients with clinically unilateral Graves ophthalmopathy the CCT scan revealed bilateral extraocular muscle enlargement In the four patients initially misdiagnosed as Graves disease CCT scan revealed metastatic breast carcinoma in one and orbital pseudotumour (Fig 2) in three

Malignancy Forty six patients had a CCT scan for suspected orbital involvement by metastatic disease or recurrence of a treated local malignancy (Table III) In 50 % of these patients the CCT scan was positive In only

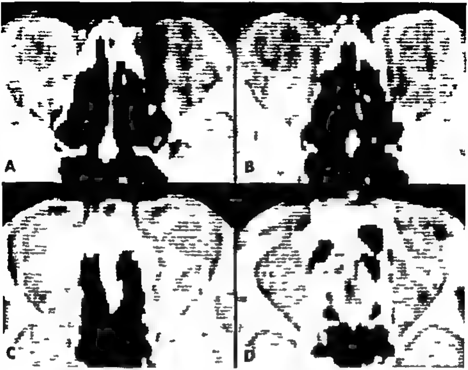

Fig 2

Fifty six year old male with six year history of bilateral proptosis caused by orbital pseudotumour CCT scan (A lowest to D highest levels) shows bilateral symmetric soft tissue densities obliterating the landmarks normally outlined by retroorbital fat Bilateral proptosis is present

two out of 23 patients with normal CCT scans was orbital metastatic disease subsequently found The CCT scan findings depended upon the tumour in question One patient in whom lymphoma had undergone leukemic transformation presented with bilateral symmetrical enlargement of extraocular muscles secondary to diffuse leukemic infiltrate The CCT scan findings resembled those of Graves disease A case of recurrent retinoblastoma previously treated by enucleation exhibited marked contrast enhancement of the soft tissue now occupying the orbit Bone destruction with abnormal soft tissue in the paranasal sinuses or nasopharynx was strongly suggestive of malignancy (Fig 3) Metastatic lesions varied in their location in the orbit Metastatic breast carcinoma however had a propensity for the medial orbit with extension anteriorly to the medial canthus (Fig 4)

Table III

CCT scan finding in 46 patients with known malignant disease and question of orbital involvement

Malignant disease	CCT scan showed mass lesion	CCT scan was normal	Total
Leukaemia	5	1	[illegible]
Hodgkin's disease	1	4	5
Lymphoma	2	5	7
Neuroblastoma	1	1	[illegible]
Metastatic adrenal carcinoma	1	–	1
Metastatic prostata carcinoma	2	1*	3
Metastatic lung carcinoma	–	1	1
Metastatic breast carcinoma	1	–	1
Metastatic retinoblastoma	1**	–	1
Metastatic squamous cell carcinoma	1	–	1
Undifferentiated carcinoma	1**	–	1
Adenocarcinoma of parotid gland	–	1*	1
Adenocarcinoma of sinuses	2	–	2
Osteogenic sarcoma	1**	–	1
Nasopharyngeal rhabdomyosarcoma	1	4	5
Fibrosarcoma	–	1	1
Malignant melanoma of ciliar body	–	1	1
Plasmacytoma	1	–	1
? recurrent retinoblastoma	1	1	2
? recurrent mixed cell tumour of the parotid gland	1	–	1
? recurrent sphenoid ridge meningioma	–	2	[illegible]
Total	23	23	46

Other examinations showed a tumour mass in the orbit

* Tumour mass found with CCT scan was located outside the orbits

The CCT scan detected malignant disease in ten patients without suspected neoplasm The clinical diagnoses in these patients prior to the CCT scan were as follows Graves disease 1 unilateral proptosis of unknown aetiology 4 eye motility problem of unknown aetiology 3 orbital pseudotumour 1 and ptotic upper eyelid of boardlike consistency 1 The primary malignant tumour in these ten patients was breast carcinoma 3 sphenoid ridge meningioma 2 adeno-

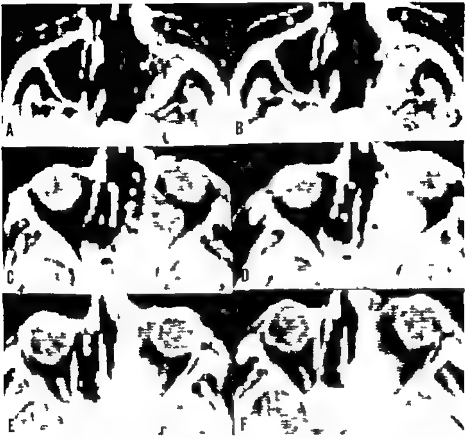

Fig 8

Seventy year old male with adenocarcinoma of the right maxillary sinus CCT scan without (A C E) and with (B D F) contrast infusion shows abnormal soft tissue density in the right maxillary antrum (A B) which extends into the ethmoidal region and inferior right orbit (C F) This mass exhibits contrast enhancement (B D F) and has resulted in bone destruction (arrow C) of the medial wall of the right maxillary antrum and right orbit

carcinoma of the lung 1 fibrosarcoma of paranasal sinus 1 orbital plasma cytoma 1 metastatic adenocarcinoma of lacrimal gland 1 and metastatic adeno carcinoma of unknown primary origin 1 Thirty six (18 %) of all patients in the present material were shown to have orbital malignant disease

Unilateral proptosis The CCT scan of twenty two patients with unilateral proptosis of unknown aetiology revealed a heterogenous group of lesions

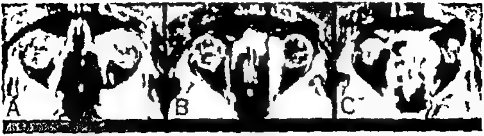

Fig 4
Sixty four year old female suspected of Graves disease but who had a metastatic breast carcinoma presenting as an extensive medial orbit mass (A B C) on the right side

Table IV
Final diagnosis in 22 patients with unilateral proptosis

Case		CCT scan finding	Final diagnosis
1	CCT scan	Retrobulbar mass	Teratoma
2	positive	Retrobulbar mass with enhancement	Haemangioma
3	(N = 16)	Retrobulbar mass with enhancement	Haemangioma
4		Soft tissue mass inflammation or exudate	Orbital cellulitis
		Retro orbital haematoma	Retro orbital haematoma
6		Graves disease	Graves disease
7		Graves disease	Graves disease
8		Graves disease	Graves disease
9		Graves disease or solitary mass	Pseudotumour
10		Abnormal scan cum proptosis not specific	Pseudotumour
11		Pseudotumour	Pseudotumour
12		Pseudotumour	Pseudotumour
13		Sphenoid ridge meningioma	Sphenoid ridge meningioma
14		Sphenoid ridge meningioma	Metastatic adenocarcinoma of sphenoid ridge
15		Retrobulbar mass	Orbital plasmacytoma
16		Soft tissue mass	Fibrosarcoma
17	CCT scan	Normal	Cavernous sinus fistula
18	negative	Normal	Orbital varix
19	(N = 9)	Normal 1st scan superior orbital mass on repeat scan	Haemangioma in the orbit
20		Normal	Unknown
21		Normal	Unknown
22		Normal	Unknown

Fig 5

Forty year old male with left proptosis caused by idiopathic orbital pseudotumour CCT scan without contrast infusion reveals a circumscribed mass lesion in the inferior left orbit (A) not present in superior level (B)

(Table IV) In 16 (73 %) of these patients the CCT scan made the diagnosis or defined a mass lesion In four patients with orbital pseudotumour two had diagnostic scans and two others had scans showing non specific mass lesions (Fig 5) Three patients with orbital haemangioma presented with a well circum scribed mass exhibiting contrast enhancement (Fig 6) A congenital orbital teratoma was the cause for proptosis in a newborn (Fig 7) The CCT scan differentiated this lesion from the main differential diagnosis haematoma which would have shown higher attenuation values and no chronic bony changes A retrobulbar haematoma was illustrated in another patient showing the ex pected high attenuation values (Fig 8)

Eye motility disturbance In nine patients with an eye motility problem of unknown aetiology the CCT scan again demonstrated a heterogenous group of lesions In five patients the CCT scan was positive Malignant disease occur red in three patients (metastatic breast carcinoma 2 sphenoid ridge menin gioma 1) One patient had Graves disease and one orbital myositis In the patient with orbital myositis the CCT scan findings were indistinguishable from the extraocular muscle enlargement seen in Graves disease

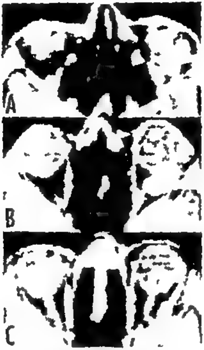

Fig 6

Sixty nine year old female with right proptosis caused by a haemangioma CCT scan shows a circumscribed mass with contrast enhancement in the infero lateral right orbit (arrow A and B) associated with enlarged lateral rectus muscle (arrow C)

Visual impairment The CCT scan was nonrevealing in nine patients with decreased vision and/or visual field defect of unknown aetiology In one patient both the clinical picture as well as the CCT scan finding showing a definitely thickened optic nerve suggested the possibility of an optic nerve sheath meningioma In seven patients with unilateral and one with bilateral optic neuritis the CCT scan was normal Four patients with optic atrophy (one with bilateral disease) had normal scans but one of these patients was shown to have an orbital haemangioma

Miscellaneous In five out of 19 patients with various symptoms the CCT scan was helpful in leading to the following diagnoses metastatic adenocarcinoma of the lung 1 metastatic adenocarcinoma of lacrimal gland 1 orbital myositis 1 haemangioma 2 and pseudotumour 1 In the 13 other patients the CCT scan was negative and further follow up has revealed no lesions

False negative CCT scans included two types of errors misinterpretation of the scan and actual lack of visualization of the lesion The missed diagnoses are discussed in greater detail

Misinterpretation Three CCT scans were initially misinterpreted The first one presented an orbital haemangioma in the superolateral part of the orbit The difficulty in interpreting the scan was due to the site of the lesion in the upper part of the orbit near the bone The second patient had a metastatic adenocarcinoma of the prostata in the sphenoid sinus The CCT scan was initially read as normal Tomograms of the sphenoid sinus showed soft tissue and bony changes Review of the CCT scan manipulating display settings showed a mass lesion in the sphenoid sinus associated with bony destruction The third patient presented with proptosis and third nerve palsy in the left eye Two CCT scans were read as normal (Fig 9) Plain radiographs of the orbits however showed asymmetry in the superior orbital fissure A left internal carotid angiogram showed a typical sphenoid ridge meningioma Review of the scans revealed several abnormalities missed because of failure to examine structures surrounding the orbit

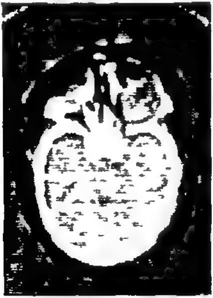

Fig 7

Right proptosis in newborn caused by teratoma CCT scan displays a large soft tissue mass occupying the right orbit resulting in marked displacement of the globe The remodeling of the bony lateral wall indicates the chronic nature of this teratoma

Fig 8

Fifty year old male with a bleeding diathesis secondary to liver disease experienced sudden proptosis and loss of vision in the right eye A dense elliptical mass (arrow A) is noted lateral to the right lateral rectus muscle causing medial displacement of this muscle and marked proptosis A repeat CCT scan several weeks after the initial scan shows partial resolution of this haematoma (arrow B)

Failure to visualize the lesion

Case 1 (cavernous haemangioma) A 65 year old white female presented with a seven year history of gradual and insidious visual loss in her left eye Corrected visual acuity in the left eye was 20/70 The left pupil with a positive swinging flashlight test was 1 mm larger than the right The left visual field showed a central scotoma and the left optic disc was slightly pale Plain skull radiographs and the orbital CCT scan were normal Optic canal tomograms revealed enlargement and erosion without sclerosis on the left Surgical exploration revealed a cavernous haemangioma in the posterior left orbit extending into the left middle fossa

Case 2 (presumed metastatic adenocarcinoma of parotid gland) A 71 year old man with known adenocarcinoma of the left parotid gland experienced the sudden onset of diplopia with pain and blurred vision in the left eye He had decreased vision in the left eye associated with left third and sixth nerve palsies The CCT scan showed only mild proptosis On the orbital venogram occlusion of the posterior portion of the left superior ophthalmic vein suggested an orbital apex metastasis but no biopsy was performed

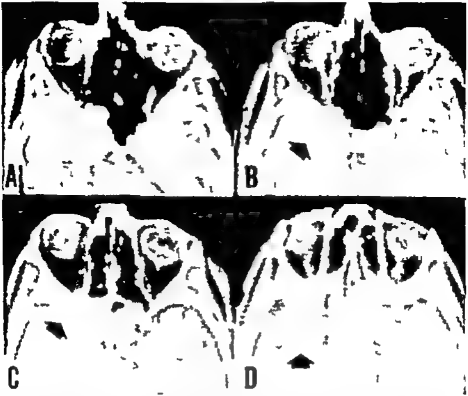

Fig 9

Sixty eight year old male presenting with diplopia mild proptosis and progressive III palsy This second CCT scan with contrast infusion shows findings indicative and characteristic of sphenoid ridge meningioma The laterally directed axis of the left globe (A B) suggests a III palsy The lack of a well defined margin of the anterior left middle fossa is secondary to contrast enhancement of this tumour (arrows B C) The posterior displacement of the left middle cerebral artery (arrow D) reflects the tumour mass anterior to it No intraorbital extension is identified

Case 3 (probable sarcoid) A 36 year old black woman with progressive visual loss in the right eye had visual acuity of 20/400 an altitudinal field defect and a positive swinging flashlight test in the right eye The right optic disc was hyperaemic The optic canal tomograms showed the right canal to be slightly enlarged The CCT scan was normal A pneumoencephalogram failed to delineate the optic nerves or chiasm well Bilateral symmetrical hilar adenopathy noted on a chest radiograph suggested the diagnosis of sarcoidosis which was confirmed by a lymph node biopsy A pre sumptive diagnosis of sarcoidosis of the optic nerve was made. Steroid therapy resulted in rapid improvement in the vision of the right eye

Case 4 (carotid cavernous sinus fistula) A 45 year old white female first complained of redness in her left eye horizontal diplopia and decreased vision The left eye had finger counting vision diffuse dilatation of the conjunctival veins severe ischaemic changes in the fundus left sixth nerve palsy and a 3 mm proptosis The CCT scan showed mild left proptosis but was otherwise normal The superior ophthalmic vein was not visualized Cerebral angiography confirmed the initial diagnosis of carotid cavernous sinus fistula

Case 5 (orbital varix) A 7½ month old baby boy was referred to be eye clinic because of right proptosis which was noted at two months of age Eye examination showed only mild proptosis puffiness in the right eye lids and an increased number of vessels in the palpebral conjunctiva The CCT scan showed mild proptosis only On re examination the child was held upside down and the diagnosis of the orbital varix was evident

Discussion

Previous studies have reported an overall accuracy of 84 % in the detection of orbital space occupying lesions (Wright et al 1975) and 72 % accuracy in the evaluation of exophthalmos (Dallow et al 1976) using the orbital CCT scan This study confirmed these previous results In grouping our patients according to their presenting clinical problems we attempted to demonstrate the usefulness of the CCT scan in certain clinical settings

In Graves disease the CCT scan demonstrated diagnostic findings in 83 % of cases and confirmed the high clinical diagnostic accuracy However several unsuspected Graves disease patients were identified and several patients thought to have Graves disease were proven to have another diagnosis Characteristic CCT scan findings were also demonstrated in two patients with Graves disease who had no eye symptoms In 92 % of the patients with orbital involvement by malignant disease the CCT scan was positive This high degree of accuracy makes a negative scan even more important in ruling out orbital involvement In 73 % of patients with unilateral proptosis and 56 % of patients with eye motility problems the CCT scan was useful in leading to the correct diagnosis

In patients with decreased vision visual field defect or optic atrophy of unknown aetiology the incidence of positive CCT scans was low Momose et al (1975) have reported a case with slight optic nerve enlargement in a patient with optic neuritis and Cala & Mastaglia (1976) claimed to have seen plaques in the optic nerves in patients with multiple sclerosis In our cases the optic nerves were carefully studied but no abnormalities were found At this time it appears that the CCT scan is useful in optic neuritis or optic atrophy only by excluding mass lesions in these patients Development of scanners with higher resolution may allow more detailed visualization of the optic nerve

Currently however only significant mass lesions of the optic nerve such as optic nerve sheath meningiomas or optic nerve gliomas are detected (Ambrose et al 1974 Gawler et al 1974 Jakobs & Kinkel 1976 Lampert et al 1974 Wright et al 1975) Our patient with presumed optic nerve sarcoidosis also demonstrated a normal CCT scan

In our study of patients with vascular malformations such as carotid cavernous sinus fistula or orbital varix the CCT scan was either negative or showed only proptosis Other studies have reported cases with arteriovenous malformations and orbital varix in which the CCT scan was helpful (Grove et al 1975 Hilal et al 1976 Leone & Wilson 1976 Momose et al 1975 Wright et al 1975) The CCT scan findings depend on the size of the malformation the presence of a haematoma or the identification of an enlarged superior ophthalmic vein

Missed diagnoses in our series were caused by either misinterpretation of scans or false negative scans In no cases did the scan miss the level of the lesion This was assured by performing complete orbital CCT scans i e a scan which included the maxillary and frontal sinuses and the inferior middle and superior orbit levels Misinterpretation resulted from lesions lying close to bone in the superior orbit or by failure to examine all the periorbital structures Although high contrast is afforded by fat within the orbit and air within the sinuses it is important to adjust the display settings especially in questions of bony involvement or in apparently negative CCT scans Vascularized lesions such as meningiomas and haemangiomas can be made more visible by contrast media The number of false negative scans will decrease with the development of higher resolution scanners but even these still need to be complemented by a good clinical examination and conventional radiographic techniques such as plain roentgenograms and angiography

A major advantage of the orbital CCT scan is the possibility of following orbital lesions thought to be benign without surgical intervention This is especially true in patients with normal vision and only mild symptoms The outcome of surgical or radiation therapy can be followed by serial CCT scans Response to steroids or radiotherapy in patients with Graves disease or orbital pseudotumour and response to chemotherapy for orbital malignancy has been monitored successfully at our institution

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References

Alper M G Davis D O & Pressman B D (1975) Use of computerized axial tomography (EMI scanner) in diagnosis of exophthalmos *Trans amer Acad Ophthal Otolaryng 79* OP-150–OP-165

Ambrose J A E Lloyd G A S & Wright J E (1974) A preliminary evaluation of fine matrix computerized axial tomography (EMI scan) in the diagnosis of orbital pace occupying lesions *Brit J Radiol 47* 747–751

Baker H L Jr Kearns T P Campbell J K & Henderson J W (1974) Computerized transaxial tomography in neuro ophthalmology *Amer J Ophthal 78* 985–994

Cala L A & Mastaglia F L (1976) Computerised axial tomography findings in multiple sclerosis *Lancet I* 689

Dallow R L Momose K J Weber A L & Wray S H (1976) Comparison of ultrasonography computerized tomography (EMI scan) and radiographic techniques in evaluation of exophthalmos *Trans amer Acad Ophthal Otolaryng 81* OP-305–OP-322

Enzmann D Donaldson S S Marshall W H & Kriss J P (1976a) Computed tomography in orbital pseudotumor (Idiopathic orbital inflammation) *Radiology 120* 597–601

Enzmann D Marshall W H Jr Rosenthal A R & Kriss J P (1976b) Computed tomography in Graves ophthalmopathy *Radiology 118* 615–620

Gawler J Sanders M D Bull J W D duBoulay G & Marshall J (1974) Computer assisted tomography in orbital disease *Brit J Ophthal 58* 571–587

Grove A S New P F J & Momose K J (1975) Computerized tomographic (CT) scanning for orbital evaluation *Trans amer Acad Ophthal Otolaryng 79* OP-137–OP 149

Hayward R W & Zatz L M (1975) A thin section collimator for the EMI scanner *Radiology 117* 475–478

Hilal S K Trokel S L & Coleman D J (1976) High resolution computerized tomography and B scan ultrasonography of the orbits *Trans amer Acad Ophthal Otolaryng 81* OP-607–OP-617

Jakobs L & Kinkel W (1976) Computerized axial transverse tomography in the diagnosis of orbital tumors *Trans amer Acad Ophthal Otolaryng 81* OP-373–OP-383

Lampert V L Zelch J V & Cohen D N (1974) Computed tomography of the orbits *Radiology 113* 351–354

Leone C R & Wilson F C (1976) Computerized axial tomography of the orbit *Ophthalmic Surgery 7* 34–44

Momose K J New P F J Grove A S Jr & Scott W R (1975) The use of computed tomography in ophthalmology *Radiology 115* 361–368

Weinstein M A Berlin A J Jr & Duchesneau P M (1976) High resolution computed tomography of the orbit with the Ohio nuclear delta head scanner *Amer J Roentgenol 127* 175–177

Wright J E Glyn A S L & Ambrose J (1975) Computerized axial tomography in the detection of orbital space occupying lesions *Amer J Ophthal 80* 78–84

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WORK AND DISABILITY AT THE AGE OF 30 YEARS

A Sociomedical Study of a Birth Cohort from Bergen
VIII Visual Impairment Frequency and Relation to School Background Intellectual Ability and Encephalopathy

BY

FINN OLAV KINGE and HENRY AASVED

The study is based on a cohort of 15,0 persons consisting of all live births in 1940 of mothers then residing in Bergen A sample was taken of the cohort after stratification according to type of school attended at the age of 14 years The sample was supplemented with persons who had either attended Special Schools for the educable mentally retarded or received care from National Services for the mentally retarded The final sample consisted of 262 persons

Persons in the sample were examined neurologically and the results of these examinations formed the basis for further ophthalmological examinations

Frequency of visual impairment in the cohort at the age of 30 years according to relatively strict criterion is estimated at 4 6 % ± 2 0 % Frequency was found to increase with a lower level of education (type of school) and decreasing IQ points Pathology of the eye was found most frequently among members of the services for the mentally retarded and was associated with encephalopathy

Key words visual acuity – visual impairment – encephalopathy – mental retardation – compulsory school

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The frequency of blindness in the Western World is assumed to be 1–2 per 1000. In a study of the population of Western Norway including all age groups, social blindness i.e. visual acuity $\leq 6/60$ was found in 2.8 per 1000 (Odland 1976). In studies of school children in the age group 9–10 years in Oslo low vision with visual acuity $\leq 6/24$ was found in 0.5 per 1000 (Holst & Tjåland 1962).

Pupils of Special Schools for the educable mentally retarded exhibit a considerably higher frequency of visual impairment than pupils of ordinary schools (Askelund 1962). Systematic investigations of the vision of persons in the National Services for the mentally retarded have not been published in Norway. However studies from other countries reveal that this group exhibits a high frequency of blindness and low vision (Warburg 1963, Copper & Schappert-Kimmijser 1970, Lindstedt 1972).

The present study focuses on the frequency of visual impairment particularly in relation to school background (type of school), intellectual ability and encephalopathy. The study is based on examinations of persons in a sample of 30 year olds taken from a cohort of persons born in the year 1940.

Material and Methods

A detailed description of the material and methods is given in a separate article (Kinge & Bjerkedal 1976). Only information relating to this study will be repeated here.

The study is based on a birth cohort of 1570 persons born in the year 1940 of mothers then residing in Bergen. The persons were followed up in the compulsory school system at the age of 14 years and again at the age of 30 years concluding as of 1st June 1971 when the situation for a total of 1535 persons (97.8 %) of the cohort was established.

A sample was taken of the cohort after stratification according to the type of school attended in Bergen at the age of 14 years. It was supplemented with persons born in the years 1937–1943 who had either attended Special Schools for the educable mentally retarded (EMR) or had received care from the National Services for the mentally retarded (SMR).

The final sample consisted of 262 persons of which 137 were males. Their distribution according to type of school attended at age 14 years is presented in Table I. Of the 262 persons 256 were still living at the age of 30 years and of these 245 were residing in Norway. A total of 225 persons were called in for interview and examination and 179 or 79.6 % participated. The procedures

Table 1

Persons in the sample[1]) at age 30 years who were ophthalmologically and otologically examined grouped according to type of school attended at age 14 years

Type of school	Adjustment factor[2])	Total number in sample	Of these examined: Neurologically	Psychologically	Ophthalmologically: Total	Of these incompl	Audiometric screening
Junior High School	0 378	47	31	30	31		26
Continuation School	0 556	64	45	45	45		44
Elementary School classes for slow learners	0 051	59	42	41	42		41
Special Schools for the educable mentally retarded	0 008	56	32	30	32	1	30
Receiving services for the mentally retarded	0 007	36	29	29	29	10	3
Total		262	179	175	179	11	144

[1]) The sample was taken after stratification of a birth cohort consisting of all live births in 1940 of mothers then residing in Bergen The sampling fractions were 10 8 % for Jr High School 10 0 % for Continuation School and 100 0 % for the other types of school and the services for the mentally retarded The sample was supplemented with persons born in 1937–43 who at the age of 14 years had resided in Bergen and were attending Special Schools for the educable mentally retarded or receiving care from National Services for the mentally retarded (SMR)

[2]) Ratio of number of persons in the respective school types receiving care from SMR respectively to the total number of persons in the birth cohort residing in Bergen at age 14 years

used with regard to completion of the examinations are described in another article (Kinge & Bjerkedal 1976)

Representativeness of those examined in relation to the total sample and to groups of pupils from the different types of school attended at the age of 14 years is evaluated on the basis of information on prenatal and perinatal risk factors in addition to results of psychological tests and school marks It can be concluded that the examined seem to be representative for the total sample as well as for the various types of schools to which they belong (Kinge 1976)

As described in another article (Kinge 1976) the participants underwent neurological electroencephalographical and psychological examinations Furthermore a pure tone audiometric screening was undertaken Based on the results of the audiometric screening the persons were referred to audiological examination (Kinge & Tonning 1976) Table I presents the number of persons in the sample who underwent the different examinations

Ophthalmological examination

The ophthalmological part of the neurological examination which was made by one of the authors (neurologist F O K) was completed for a total of 168 of the 179 participants For the remaining 11 all of whom were mentally retarded examinations of visual field were incomplete due to lack of co operation (Table I)

A total of eight ametropics whose visual acuity was normalized on correction with glasses had recently been examined by an ophthalmologist Results of these examinations are included in this study The remaining persons with visual acuity less than 6/6 in at least one eye were examined by one of the authors (ophthalmologist H Aa) This also applied to persons with other positive or questionable findings in the eye status Of the 179 persons examined a total of 51 (28 5 %) were referred and of these 50 participated

The subjective method was applied for the refractive examination However retinoscopy was used in examining some of the mentally retarded persons

Results

Results of the ophthalmological examination are summarized in Table II Frequencies of positive findings i e ametropia and pathology are given for those examined according to the type of school attended at the age of 14 years Frequencies adjusted to the birth cohort as a whole (adjustment factor is given

Refraction errors and pathology found by ophthalmological exam [illegible]

type of school attended at age 14 years

Type of school	Total number exam	Of these Number/Per cent with positive findings one or both eyes						
		Refract errors corr vis ac 6/6 o u	Visual impairment				Strabismus	Other[1]
			Total	Corr visual acuity				
				6/9–6/12	6/18–6/60	< 6/60		
Jr High and Continuation Schools	76	15 19 7	3 4 0	2	1	0	1	0
Elementary School el for slow learn	42	0 0 0	4 9 5	4	0	0	0	0
Special Schools for the EMR)	3? (1)	3 9 7	8 25 8	4	1	3	7	2
Receiving serv for the ment retarded	29 (10)	? 10 5	6 31 6	0	4	2	7	5
Total number	179 (11)	0	21	10	6	5	15	7
Per cent adjusted to birth cohort		18 3	4 6	3 1	1 4	0 1	1 6	0 ?
Est stand dev		4 ?	2 0				1 6	1 6

The figures in parentheses indicate the incompletely examined Percentage of refraction errors and visual impairment are based on those who are completely examined

[1] Include optic nerve atrophy/oculomotor lesion (1 person) subluxation of the lens (1) cataract (?) exce sive myopia with retinal degenera tions (?) and gaze paresis (1)

) EMR Educable mentally retarded

in Table I) are also included. In the present study corrected visual acuity 6/9 or less in the weakest eye indicates visual impairment.

The refraction errors with corrected visual acuity 6/6 o.u. are all moderate with refraction up to ± 5.0 dioptrics. Latent hypermetropia is not included. The frequencies of refraction errors (Table II) are highest for former pupils of Junior High and Continuation Schools with a total of 19.7 % (15 of 76) and lowest for former pupils of Elementary School classes for slow learners, surprisingly 0 % (0 of 42). The frequency for the members of SMR is based on the 19 persons completely examined. The frequency of ametropia for the cohort as a whole is estimated to 18.5 % with an estimated standard deviation of ± 4.2 %.

The frequency of *visual impairment* increases with a "lower" level type of school from 4.0 % (3 of 76) for former pupils of Junior High and Continuation Schools and 9.5 % (4 of 42) for Elementary School classes for slow learners to 25.8 % (8 of 31) for Special Schools for the EMR and 31.6 % (6 of 19) for the members of SMR. The difference in frequency of visual impairment on

Table III

Main cause of visual impairment and/or refraction errors for those in the sample who were examined at age 30 years grouped according to corrected visual acuity of the weakest eye

Correct visual acuity weakest eye	Total number with visual impairm and/or refr errors uncorr	Of these: Number with main cause					
		Myopia	Hyper metropia	Astig matism	Ambly opia/ strabis mus	Ambly opia/ aniso metropia	Other causes[1]
6/6	20	15	1	4	–	–	0
6/9–6/12	10	0	0	7	2	1	0
6/18–6/60	6				4	0	2
< 6/60	5				2	0	3
Total	41	15	1	11	8	1	5

[1] Includes optic nerve atrophy (1 person), subluxation of the lens (1), cataract (1), excessive myopia with retinal degenerations (2).

Table IV

Persons with visual impairment of those in the sample who were psychologically and completely ophthalmologically examined grouped according to IQ points (WAIS total test score)

IQ points	Total number psych examin	Of which compl ophthalm examin	Of these with visual impairment			
			Total number	Per cent	Corr visual acuity	
					6/9–6/12	< 6/12
> 90	87	87	3	3 4	[illegible]	1
76–90	33	33	5	15 2	4	1
56–75	[illegible]	28	5	17 9	3	[illegible]
< 56	27	18	8	44 4	1	7
Total	175	166	21	–	10	11

As the percentage is determined by the composition of the sample this is not given here

one hand for former pupils of Elementary School classes for slow learners and Special Schools for the EMR and for members of SMR and on the other hand for pupils of Junior High and Continuation Schools is statistically significant ($\chi = 7\ 91$ $P < 0\ 01$)

In accordance with information from the SMR and observations during the medical examination none of the 11 persons incompletely examined had apparent sight problems

A total of three persons completely examined had a visual acuity less than 6/60 in the best eye Of these one was amaurotic and a former pupil of the Special Schools for the EMR while the remaining two with social blindness were members of SMR

The frequency of visual impairment for the cohort as a whole is estimated at 4 6 % with an estimated standard deviation of 2 0 % The frequency of *strabismus* is considerably higher among members of SMR with 24 1 % (7 of 29) and former pupils of Special Schools for EMR with 21 9 % (7 of 32) than in other types of schools In Elementary School classes for slow learners 0 % (0 of 42) and in Junior High and Continuation Schools 1 3 % (1 of 76) have strabismus

The difference in frequency of strabismus among members of SMR and former pupils of Special Schools for EMR when contrasted with former pupils of the other types of schools is statistically significant ($\chi = 22\ 79$ $P < 0\ 001$)

Other specified *pathological findings* are also found to be concentrated in the SMR and EMR groups (Table II).

The frequency of strabismus for the cohort as a whole is estimated to 1.6 %, with a standard deviation of 1.6 %.

Main causes of visual impairment including refraction errors are tabulated in Table III according to corrected visual acuity in the weakest eye. In cases of combined refraction errors with spherical and astigmatic ametropia that type of ametropia was chosen which was considered to be the most important. Of the refraction errors myopia is in majority (15 of 20 cases). Considerable cornea astigmatism is assumed to be the cause of slight visual impairment in seven persons. Of a total of 15 persons with strabismus eight have amblyopia (Tables II and III). They were all former pupils of Special Schools for EMR or members of SMR.

Visual impairment and IQ. Table IV presents frequencies of visual impairment according to IQ points (WAIS – total test score) among persons completely ophthalmologically examined who were also psychologically tested. The percentage with visual impairment in the various IQ groups increases with decreasing IQ points from 3.4 (3 of 87) for the group IQ $>$ 90 to 44.4 (8 of 18) for the group IQ $<$ 56. The difference in frequency of visual impairment in the group IQ $\leq$ 90 and the group $>$ 90 is statistically significant ($\chi^2 = 19.31$, $P < 0.001$).

Table V

The correlation between visual impairment and the diagnosis of encephalopathy[1] for those in the sample who were neurologically and completely ophthalmologically examined

Corr. visual acuity weakest eye	Total number examined	Of these No. and per cent with encephalopathy		
		Definite	Possible	Negative
6/6	147	12 8.2	15 10.2	120 81.6
≥ 6/9	21	8 38.1	3 14.3	10 47.6
Total	168	20 *	18 *	130 *

[1] Based on neurological and electroencephalographical examination and the symptom epilepsy.

* As the percentage is dependent on the composition of the sample it may be misleading and is therefore not given.

Table VI

Visual and hearing impairment for those in the sample at age 30 years who were examined completely ophthalmologically and audiometrically screened grouped according to type of school attended at age 14 years

Type of school	Total number examined	Of these Number and per cent with visual/hearing impairment		
		Only visual	Only hearing	Visual and hearing
Jr High and Continuation Schools	70	2 29	11 15 7	1 14
Elementary School cl for slow learn.	41	3 7 3	7 17 1	1 24
Special Schools for the EMR[1]	30	6 20 0	8 26 7	2 6 7
Receiving serv for the ment retarded	3	3	0	0
Total number	144	14	26	4
Per cent adjusted to birth cohort		3 3	16 0	1 5
Est stand dev		1 8	4 0	1 8

[1] EMR Educable mentally retarded

Visual impairment and encephalopathy Of those completely ophthalmologically examined who were found to have visual impairment 52 4 % (11 of 21) had definite or possible encephalopathy compared to 18 4 % (27 of 147) in the group with normal corrected visual acuity (Table V) The difference in frequency of definite and possible encephalopathy in these two groups is statistically significant ($\chi = 10\ 28$ $P < 0\ 01$) Strabismus is a common cause of visual impairment as mentioned earlier (Table III) Of those found to have strabismus 67 7 % (10 of 15) had definite or possible encephalopathy compared to 22 6 % (37 of 164) of those without strabismus

Combined visual and hearing impairment Table VI presents frequencies of combined visual and hearing impairment according to type of school attended

at the age of 14 years among persons in the sample who were completely ophthalmologically examined and audiometrically screened. Isolated hearing impairment dominates in Junior High and Continuation Schools as well as in Elementary School classes for slow learners, whereas percentages with isolated visual and hearing impairments are of the same magnitude in Special Schools for the EMR. Percentages with combined visual and hearing impairment are the smallest in all types of schools.

The frequency of combined visual and hearing impairment for the cohort as a whole is 1.5 % with an estimated standard deviation of 1.8 %. The corresponding figures for isolated visual or hearing impairment are 3.3 % ± 1.8 % and 16.0 % ± 4.0 % respectively.

Discussion

In the present study, visual impairment means a failure in the total visual function. Failure in one eye is considered a visual impairment even when the other sense organ is functioning normally. Undoubtedly unilateral hearing loss may lead to communication problems (Giolas & Wark 1967), whereas a moderate reduced visual acuity in one eye scarcely represents any social problem.

The criterion used for determining the presence of visual impairment is well defined and relatively strict. No attempt is made to evaluate the practical consequences of a failure in the visual function because of the complexity of the problems involved. In fact, practical consequences are not only dependent on the degree of the visual failure, but other factors such as mental capacity are also of essential importance. For example the same failure in the visual function is assumed to be more restrictive for a mentally retarded person than for a person with a higher mental capacity.

In summary: The frequency of visual impairment at the age of 30 years is estimated to be 4.6 % ± 2.0 %. Frequency tends to increase with a lower level type of school and is especially high for former pupils of Special Schools for the EMR with 25.8 %. The ophthalmological examination of members of SMR reveals a high frequency of pathological findings. These are associated with the presence of encephalopathy. Visual impairment is more frequent in the group with IQ points less than 90 than in the group with IQ points above this level.

The uncertainty attached to the frequencies estimated for the cohort as a whole, as indicated by the standard deviations, is not only related to the size of the sample, but also to the incomplete examination of some of the persons

in the sample. The incomplete ophthalmological examination of members of SMR will however have little influence on the estimate of the frequency of the cohort as a whole since the proportion of the cohort receiving SMR is so small (Table I).

The *refraction errors* which can be corrected to normal visual acuity are not defined as visual impairment. Frequency of these refraction errors for the cohort is estimated at 18.3 %. Latent hypermetropia is not included in this estimate since persons who were found to have a normal visual acuity when neurologically examined were not further ophthalmologically examined.

Refraction errors seem to be included as *visual impairment* in several investigations. This is the case in previous investigations of pupils from the Special Schools for the EMR in Norway (Askelund 1962), where the frequency of visual impairment was found to be 33.9 % (20 of 59) and 45.7 % (16 of 35) in two investigations. Percentage of visual impairment including refraction errors for the corresponding group in the present study would be 35.5 % (11 of 31 – Table II).

The ophthalmological examination of members of SMR reveals a high frequency of pathological findings. These findings include both visual impairment (31.6 %), strabismus (24.1 %) and other findings (total 17.2 %). Other investigations of the mentally retarded report high frequencies of pathological findings in the eye, especially optic nerve atrophy (Copper & Schappert-Kimmijser 1970, Lindstedt 1972). Reports from institutions in Denmark for members of SMR indicate that the frequency of blindness among these persons is 40–80 times higher and the frequency of low vision 30–120 times higher than in the normal population (Warburg 1963, 1966).

It is reasonable to explain the association between visual impairment and type of school attended at the age of 14 years on the basis of the increasing frequency of encephalopathy with a "lower" level type of school (Kinge 1976). The association between visual impairment/other pathological findings in the eye and encephalopathy is evident. Such an association is to be expected on account of the intimate developmental relationship between the central nervous system and parts of the visual apparatus.

Frequency of hearing impairment in the cohort is estimated at 17.5 % ± 4.2 % (Kinge & Tonning 1976). Like visual impairment the frequency of hearing impairment is especially high among the mentally retarded. Therefore, with the intention of reducing or preventing these important additional handicaps among the mentally retarded, ophthalmological and otological evaluation is essential. Corrective measures must start as early as possible, at all events before entering compulsory schools or registration in Services for the mentally retarded.

References

Askelund P (1969) Synsundersokelser av barn ved spesialskolene (Testing of vision in children in special schools) T norske Lægeforen (J Norweg Med Ass) 89 11 II (Summary in English)

Copper A C & Schappert Kimmijser J (1970) The causes of blindness in 156 visually and mentally defective children Ophthalmologica 160 292–307

Giolas T G & Wark D J (1967) Communication problems associated with unilateral hearing loss J Speech Hear Disord 32 336–343

Holst J C & Tjåland J (1962) Noen tall fra skoleøyelægekontoret i Oslo T norske Lægeforen (J Norweg Med Ass) 82 1291–1293

Kinge F O & Bjerkedal T (1976) Work and disability at the age of 30 years I Description of project and methods Scand J Soc Med (in press)

Kinge F O (1976) Work and disability at the age of 30 years VII Encephalopathy frequency and relation to school background and intellectual ability Acta Neurol Scand (in press)

Kinge F O & Tonning F (1976) Work and disability at the age of 30 years IX Hearing impairment frequency and relation to school background intellectual ability and encephalopathy Scand Audiol (in press)

Lindstedt Eva (1972) Severe visual impairment in Swedish children Docum ophthal 31 173–204

Odland M (1977) Svaksyn og blindhet i Bergen og Hordaland En medisinsk og sosial medisinsk undersokelse (Thesis Univ of Bergen)

Warburg Mette (1963) Diseases for the eye among mental defectives Acta ophthal (Kbh) 41 157–165

Warburg Mette (1966) Behovet for oftalmologisk service på en institution for åndssvage Ugeskr Læg 128 437–439

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MORPHOLOGY OF MOTOR UNITS IN CAT EXTRAOCULAR MUSCLE

BY

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Muscle fibers from single motor units in cat inferior oblique were marked iontophoretically with procion red injected through an intracellular pipette The fibers were isolated by dissection and characterized by electron micro scopy A fiber in a slow motor unit with non conducted electrical responses showed slow fiber morphology of the amphibia type Fast twitch motor units contained fibers with twitch fiber morphology Thus a good cor relation between muscle fiber structure and function was obtained in these eye motor units examined with both physiological and morphological techniques

Key words extraocular muscle – cat – electron microscopy – slow and fast fibers

Morphological and physiological studies by Hess & Pilar (1963) indicated that the cat superior oblique muscle contains slow muscle fibers similar to those in amphibian muscle (Kuffler & Vaughan Williams 1953 Peachey & Huxley 1969) Such fibers have multiple (en grappe) innervation They do not pro pagate action potentials The contractions of these fibers are induced by local depolarizations at the multiple nerve terminals evenly distributed over the muscle fiber membrane Due to a scanty sarcoplasmic reticulum and a poorly developed tubular system the spread of excitation inside the fiber is probably

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less efficient than in other types of muscle fibers and this may be one reason why the contractions are slower than for any other fiber system Recently extensive studies of fiber ultrastructure and innervation have shown that amphibia type multiply innervated fibers occur in cat extraocular muscle (Alvarado & van Horn 1975 Alvarado 1977)

Bach y Rita & Ito (1966) were unable to confirm the findings of Hess & Pilar (1963) in their physiological study of cat inferior oblique and superior rectus muscles They suggested that the slow muscle fibers were of twitch type i e the fibers were able to conduct impulses although they concurred that the fibers were probably multiply innervated However Alvarado and co workers have now found a second morphologically distinct multiply innervated fiber (Alvarado 1977)

In a study of single motor units in the inferior oblique muscle Lennerstrand (1974) was able to isolate a few units with physiological characteristics of amphibian slow fibers This preliminary report describes the electron microscopic appearance of a muscle fiber isolated from one of these units It was found to be of the amphibia type described by Alvarado and co workers (1975 1977)

The morphology of fibers from four units with fast contractions and conducted impulse activity will also be briefly presented They had the structural characteristics of fast twitch fibers (Alvarado et al 1975 1977) with nerve terminals restricted to one area (focal innervation) and much more extensive sarcoplasmic reticulum and transverse system than slow fibers

Methods

The techniques used 1) for isolating motor units in the inferior oblique muscle 2) for introducing dye intracellularly in the fibers of single units and 3) for preparing these fibers for electron microscopy have been fully presented in papers by Lennerstrand (1974) and Bach y Rita (1975) and will only be briefly described here

In adult cats the tendon of the inferior oblique muscle was attached to a sensitive device for isometric tension recording By stimulating thin filaments of the muscle nerve single motor units could be activated In addition to mechanical responses from the units their electrical responses were recorded extracellularly from the surface of the muscle and intracellularly in muscle fibers belonging to the unit under study Intracellular recordings were performed in three fibers of one of the slow and in fibers of several of the fast units (Lennerstrand 1974) These fibers were marked iontophoretically with procion red Only a few fibers could be successfully characterized by electron microscopy

Figs 1 a and b

a Longitudinal section of the slow fiber showing very few mitochondria (M) a scanty membranous system and thick z line 18 500 × magnification (bar indicates 1 μm)

b Longitudinal section of a (type 2) fiber from a fast motor unit with moderate number of mitochondria (M) well developed sarcoplasmic reticulum (arrows) and thin z line 19 000 × magnification (bar represents 1 μm)

Results

Lennerstrand (1974) studied approximately 100 single units in the inferior oblique muscle Five of these were slow units with the physiological properties described below The muscle fiber shown in Fig 1 a was obtained from such a unit The mechanical and electrical responses of this unit have already been presented (Lennerstrand 1974 Fig 1 B and C Fig 3 D) It was shown that the unit had no twitch response to single pulse stimulation and had a very slowly rising tension to tetanic nerve stimulation The tension curve fused at a stimulus rate of 60 Hz No conducted electrical activity but only additive local responses could be recorded extracellularly Intracellular recordings from three muscle fibers in this units revealed resting potentials around 50 mV indicating that they had not been injured by the recording electrode On stimulation of the nerve very small membrane potential changes were generated in the muscle fibers and no action potentials were fired even to repetitive stimulation Clearly this slowly contracting unit was composed of non conducting fibers with a strong physiological resemblance to slow muscle fibers in amphibian muscle One of the fibers was successfully characterized by electron microscopy (Fig 1 a) It had relatively small infrequent mitochondria The myofibrils were closely opposed barely separated from each other by sparse sarcoplasmic reticulum The system of transverse tubules was poorly developed The fiber was also characterized by a thick z band It corresponded to the fiber type 4 in the classification of Alvarado & van Horn (1975) resembling amphibian slow muscle fibers

In addition to this slow motor unit four fast units were analyzed with regard to muscle fiber morphology The twitch contraction times of these units were between 6 and 10 msec which is within the range of fast eye motor units (Lennerstrand 1974) Their muscle fibers propagated action potentials as revealed in extra and intracellular recordings In three of the units intracellular recordings were made from two or more muscle fibers For each unit resting potentials and responses to nerve stimulation were very similar in all of its fibers *Physiologically these fibers were fast twitch fibers*

In one of these units two fibers were identified by electron microscopy They had both the same appearance with focal innervation and moderately developed tubular system and sarcoplasmic reticulum They correspond to the type 3 fiber in the classification of Alvarado & van Horn (1975) One of the other units also contained a type 3 fiber One fiber in each of the remaining two units could be examined with the electron microscope Both of them had focal innervation but they were larger in size hade a more extensive tubular system and sarcoplasmic reticulum and fewer and smaller mitochondria than the type

3 fibers As in the type 3 fibers the z line was thinner than in the type 4 fiber of the slow unit These last two fibers correspond to the type 2 fiber of Alvarado & van Horn (1975) One of the fibers is shown in Fig 1 b

Discussion

This is the first study to correlate physiological and morphological properties of muscle fibers in single motor units of extraocular muscle One slow motor unit with the physiological characteristics of amphibian slow muscle has been shown to have the morphology of such slow fibers We have considered it justified to present data from only one but nevertheless well documented unit because of 1) the controversy that has existed over the properties of slow fibers in cat extraocular muscle and 2) the great difficulties in isolating slow motor units and subsequently studying their fibers by electron microscopy

Morphologically this fiber fell distinctly within the group of type 4 fibers (amphibia like) in the classification made by Alvarado and van Horn (1975)

Intracellular microelectrode recordings were made from three fibers in this slow unit but only one fiber could be examined morphologically Physiologically all three fibers were similar they had the same resting potentials and none of them fired action potentials All three fibers thus seemed to be of the same type physiologically and probably also morphologically This notion is supported by studies of motor units in other muscle where each unit is known to consist of the same type of fibers (Burke et al 1973 Edstrom & Kugelberg 1968) and by the finding in this study that two fibers isolated in a fast unit were of the same morphological type

The study by Lennerstrand (1974) suggested that some of the motor units consisted of multiply innervated conducting fibers resembling the slow twitch fibers demonstrated physiologically by Bach y Rita & Ito (1966) Unfortunately no fiber from such units has successfully been carried through all the steps necessary for electron microscopic examination We therefore do not know the ultrastructure of the slow twitch fibers and can only infer the physiologic properties from known morphologic characters of multiply innervated fiber types (see Bach y Rita 1975)

Muscle fibers of four fast units were examined electron microscopically Two of the units were found to contain muscle fibers of type 2 and two had type 3 fibers according to the classification of Alvarado & van Horn (1975) These authors have suggested on morphological grounds that the focally innervated type 2 and 3 fibers with their well developed sarcoplasmic reticulum and transverse tubules should be expected to be fast contracting and impulse conducting Thus a good correlation between physiology and morphology seems to exist also in the fast units

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References

Alvarado J A & van Horn C (1975) Muscle cell types of the cat inferior oblique In Lennerstrand G and Bach y Rita P Eds *Basic Mechanisms of Ocular Motility and Their Clinical Implications* Pergamon Press Oxford pp 15–43

Alvarado J (19[illegible]7) Personal communication

Bach y Rita P (19[illegible]5) Structural functional correlations in eye muscle fibers eye muscle proprioception In Lennerstrand G and Bach y Rita P Eds *Basic Mechanisms of Ocular Motility and Their Clinical Implications* Pergamon Press Oxford pp 91–109

Bach y Rita P & Ito F (1966) *In vivo* studies on fast and slow muscle fibers in cat extraocular muscles *J gen Physiol 49* 1177–1198

Burke R E Levine D N Tsairis P & Zajac III F E (1973) Physiological types and histochemical profiles in motor units of the cat gastrocnemius *J Physiol (Lond) [illegible]34* 23–[illegible]48

Edstrom L & Kugelberg E (1968) Histochemical composition distribution of fibers and fatiguability of single motor units *J Neurol Neurosurg Psychiat 31* 4[illegible]4–431

Hess A & Pilar G (1963) Slow fibers in the extraocular muscles of the cat *J Physiol (Lond) 169* [illegible]80–797

Kuffler S W & Vaughan Williams E M (1953) Properties of the slow skeletal muscle fibers of the frog *J Physiol (Lond) 121* 318–340

Lennerstrand G (19[illegible]4) Electrical activity and isometric tension in motor units of the cat s inferior oblique muscle *Acta physiol scand 91* 4[illegible]8–474

Peachey L D & Huxley A F (1962) Structural identification of twitch and slow striated fibers of the frog *J Cell Biol 13* 1[illegible]7–180

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OCULAR HERPES SIMPLEX INFECTION A CLINICAL EVALUATION OF VIRUS ISOLATION AND STUDIES ON IODO DEOXYURIDINE RESISTANCE

BY

L NORDENFELT and E NORDENFELT

Fifty seven patients with ocular herpes simplex (HS) infection were studied for evaluation of existing methods for virus isolation and its application in diagnosis of HS infection Virus was isolated in 90 % of 34 cases with keratitis dendritica when specimens were taken within eight days of onset of symptoms The same isolation frequency was obtained in 10 cases of palpebral herpes with conjunctivitis No isolation was possible in 11 cases of keratitis disciformis Laboratory confirmation was obtained within four days in 70 % of the positive cases Ten strains of HS virus type 1 were examined for IDU resistance 5 strains isolated prior to and 5 during IDU treatment Nine of the strains had the same degree of sensitivity One strain isolated during treatment was found to be highly resistant

Key words ocular herpes simplex – virus isolation – IDU resistance

Treatment of ocular herpes simplex (HS) infection is still a problem Kaufman introduced 5 iodo 2 deoxyuridine (IDU) in 1962 as an antiviral compound for these infections (Kaufman 1962) Several investigations have shown its clinical value (Kaufman 1965) and IDU is often a preferable treatment in combination with traditional treatment like abrasio corneae and cauterization

The clinically IDU resistant cases pose a special problem and the question arises as to whether IDU resistant strains of HS virus have developed *In vitro*

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studies have shown that such strains can easily develop (Buthala 1964). Clinical reports have stated the existence of resistant strains in single cases (Laibson et al. 1963, Pavan-Langston et al. 1972). Because of these findings it has been assumed that IDU resistance is one important cause of therapy failure. This however is a moot point (Jawetz et al. 1970).

Besides IDU, several other anti-viral compounds have been tested and are being introduced as alternatives in treatment of ocular HS infections (Kaufman 1976). The present investigation was made in order to study existing methods for virus isolation in diagnosis of ocular HS infection in view of the need for laboratory diagnosis in evaluating anti-viral drugs during testing. Furthermore a study was done on IDU resistance in HS strains isolated prior to and during IDU treatment.

Material

The material consisted of 57 patients with the preliminary diagnosis of ocular HS infection. They were close to the total number of patients treated for this disease as out-patients as well as in-patients at the Eye Clinic, University Hospital of Lund, during an eighteen month period. The patients were divided into different groups according to the clinical picture. Thirty-four had a keratitis with typical dendritical lesions of the epithelium, 10 patients had vesicular eruptions on the lids with conjunctivitis and 11 cases had keratitis disciformis with blurring of the stroma. Two cases had a keratitis with punctata lesions of unspecific type. Three patients had a recurrence of infection during the time of investigation. The recurrences were regarded as separate cases.

Ten strains of isolated HS virus were examined for resistance to IDU. Five strains were isolated before start of therapy. Five were isolated during IDU treatment.

Methods

In most cases the first specimen was obtained at the first examination after start of symptoms. Cauterization or abrasio corneae was not performed until after the specimens had been obtained.

At the start of the investigation specimens were obtained both by scraping the cornea and by turning a cotton-tipped swab in the lower fornix. The isolation frequency was the same with both procedures. During the main part of the investigation the specimens were obtained with the swab, because of the ease and harmlessness of this technique.

A trypton broth was used as a transport medium The specimen tubes were stored in a refrigerator at +4°C and were brought to the virus laboratory once every weekday

Isolation procedures

Before inoculation of the specimens penicillin and streptomycin were added If immediate inoculation could not be carried out the samples were frozen at –70°C

Cell cultures in roller tubes were prepared from GMK (green monkey kidney) cells (Flow laboratories Irvine Scotland) MAS (cell line established from human bone marrow) cells (Kjellen 1961) and human embryonic diploid lung fibroblasts (HFL) prepared in our laboratory Inoculation of specimens was made in duplicate roller culture tubes which were incubated at 37°C and observed three times weekly for cytopathic effect (CPE) Cultures showing no CPE within 14 days of incubation were discarded as negative No blind passages were made Typing was done by neutralization tests in roller culture tubes using guinea pig antisera obtained from the National Bacteriological Laboratory Stockholm Sweden

Evaluation of the in vitro sensitivity of isolated herpes simplex strains

Virus strains were taken from the first passage after isolation and stored at –60°C 0 2 ml of a dilution of 10 was inoculated in eight Carrell culture bottles Two days prior to inoculation the bottles were seeded with 10^5 HEL cells/ml (Medium MEM 10 % foetal calf serum Flow lab Irvine Scotland) At the time of inoculation the medium was changed and two bottles each received MEM with 2 % foetal calf with IDU (Ferring Malmo Sweden) at concentrations of 75 50 25 and 0 μg/ml After two days all bottles were frozen and virus concentration from the different bottles was determined by titration in roller tube cultures of HFL cells with five tubes in each dilution The titration end point was read after three days and 50 % tissue culture infective dose ($TCID_{50}$) was determined according to the Reed Muench formula

Results

In 57 patients with the preliminary diagnosis of ocular HS infection HS virus type 1 was isolated in 30 cases (Table I) A preliminary laboratory answer of these positive isolations was obtained within 2–3 days in 40 % and within 4 days in 70 % and the rest within a week

Table I

Final diagnosis and relation to virus isolation in 57 patients with preliminary diagnosis ocular herpes simplex infection

Diagnosis	Number of patients	Positive isolations
Keratitis dendritica	34	21
Palpebral herpes with conjunctivitis	10	9
Keratitis disciformis	11	0
Atypical keratitis	2	0
	57	30

Of the 57 patients 34 had a final diagnosis of keratitis dendritica and virus was isolated in 21 cases The frequency of positive isolation was influenced by the time when specimens were taken after the first symptoms and by the fact that in some cases treatment with IDU was started before specimens were obtained (Table II) If specimens were taken within eight days of the first symptoms and no treatment had been provided 90 % of the cases were positive (18 of 20 cases)

Table II

Result of isolation trials in 34 patients with keratitis dendritica with regard to time after first symptoms and eventual IDU treatment prior to isolation

	1–8 days no IDU treatment	1–8 days IDU treatment	> 8 days with or without treatment
Positive	18	3	0
Negative	2	6	5
	20	9	5
		Total 34	

There were 10 patients with the diagnosis of palpebral herpes with conjunctivitis In nine cases virus was isolated Clinical diagnosis was made on the basis of symptoms of conjunctivitis with vesicular eruptions on the lids None had developed keratitis before isolation Half of the cases developed corneal epithelial lesions a few days after isolation

There were 11 cases with the final diagnosis of keratitis disciformis Clinical diagnosis was made from blurring of the stroma as well as oedema of the epithelium There was a history of keratitis dendritica in all cases No case with actual lesions typical of dendritica was referred to this group In no case virus was isolated

The remaining two cases had the preliminary diagnosis of keratitis herpetica? There was a history of earlier incidents Subjectively the symptoms were discomfort and objectively fluorescein staining punctata lesions of unspecific type They healed in a couple of days

In nine cases with positive virus isolation repeated isolations were done In five cases these were positive Re isolation was done in four of these cases within eight days In one case virus was isolated 4 times four days apart during IDU treatment This patient suffered from leukaemia at a late stage Treatment with IDU was begun after the first isolation in all cases

Ten strains from 10 patients were studied for their *in vitro* sensitivity to IDU Five strains were isolated from patients who had not been treated with

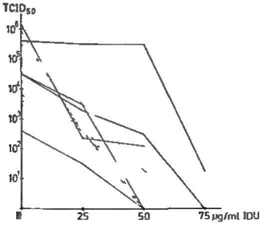

Fig 1

Titer of ten strains of herpes simplex virus isolated prior to and during IDU treatment grown in 0 25 50 and 75 ug/ml IDU

- - - - - strains isolated prior to IDU treament

——— strains isolated during IDU treatment

IDU and five were isolations done from patients during 4–6 times treatment with IDU daily These patients were treated for 2 4 5 7 and 12 days

Nine of the strains had the same degree of sensitivity and showed a 90 % or more reduction of infectivity already at 25 μg/ml IDU (Fig 1) whether the isolation was done prior to or during IDU treatment One strain isolated after seven days of IDU treatment was not inhibited even by 50 μg/ml a pattern distinctly different from the others (Fig 1) From this patient an earlier isolate was available showing the same high degree of resistance to IDU This isolation was done before IDU treatment was started

Discussion

The investigation showed that existing methods for virus isolation are useful in diagnosis of ocular HS infections In the majority of cases there was a positive laboratory confirmation in four days or earlier Duration of symptoms and treatment with IDU affects the frequency of isolation In patients without IDU treatment and with duration of symptoms less than eight days the frequency of isolation was 18 of 20 (90 %) This is in agreement with earlier findings by Coleman et al (1969) who found the highest isolation frequency (62 %) in this group of patients Generally it was no problem to establish the diagnosis in this particular type of ocular HS infection but there is an advantage in using a reliable and fast isolation procedure when evaluating new antiviral agents

In the cases with palpebral herpes with conjunctivitis there is a greater interest in aides to obtain the correct diagnosis This type is common among children and there are problems in differentiating for instance against impetigo contagiosum Virus was isolated in 9 cases out of 10 although there were no corneal lesions Treatment with IDU was begun after positive isolation Only one case progressed to a classic dendritical lesion

The group of keratitis disciformis is a type of ocular HS infection where the differential diagnosis presents a problem if there is no earlier incident of herpetic keratitis and the symptoms are unspecific In agreement with other reports (Coleman et al 1969) we were unable to isolate virus in this deep stromal type of keratitis

At present very few data are available as to the emergence of drug resistant virus in man (Oxford 1976) *In vitro* studies have shown that resistant HS virus could easily be obtained by serial passage of the virus in cell culture in the presence of IDU (Buthala 1964) In agreement with this *in vivo* studies in rabbits showed that 3 out of 4 isolates from corneal epithelium of eyes previously treated with IDU were highly resistant to IDU *in vitro* (Underwood et al 1965)

Single strains of herpes simplex isolated from clinical cases have been reported resistant to IDU when tested *in vitro* (Laibson 1963 Pavan Langston 1972) Because of these reports it has been assumed that IDU resistance is one important cause of therapy failure

True drug resistance in unresponsive herpes keratitis however has not often been studied In one investigation 12 HS strains from clinically IDU resistant patients were examined for drug susceptibility in cell culture (Jawetz et al 1970) Ten out of the 12 isolates were equally sensitive to IDU and two isolates were 10 to 30 times more resistant

In our investigation 4 out of 5 strains isolated during IDU treatment were as sensitive to IDU as five strains isolated before treatment The one resistant strain was highly resistant to IDU but the same resistance was obtained in an earlier isolate from the same patient before IDU treatment was started Our results indicate that IDU resistance *in vivo* does not appear very easily

The frequency of resistance seems to be the same today as reported earlier (Jawetz et al 1970) in spite of frequent use of IDU Therapy failure may be caused by other factors such as impaired immunological capacity In this investigation this is shown by the leukaemia case In spite of full IDU treatment during 12 days in hospital an IDU sensitive HS strain was isolated

References

Buthala D A (1964) Cell culture studies on antiviral agents Action of cytosine arabinoside and some comparison with 5 iodo 2 deoxyuridine *Proc Soc exp Biol (N Y) 115* 69–77

Coleman V R Thygeson P Dawson Ch & Jawetz E (1969) Isolation of virus from herpetic keratitis *Arch Ophthal (Chicago) 81* 22–24

Jawetz E Coleman V R Dawson C R & Thygeson P (1970) The dynamics of IUDR action in herpetic keratitis and the emergence of IUDR resistance *in vivo* *Ann N Y Acad Sci 173* 282–289

Kaufman M E Nesburn A B & Maloney E D (196) IDU therapy of herpes simplex *Arch Ophthal (Chicago) 67* 583–591

Kaufman M E (1965) Problems in virus chemotherapy *Progr med Virol 7* 116–159

Kaufman M E (1976) Ocular antiviral therapy in perspective *J infect Dis 133* (Suppl) A 96 A 100

Kjellen L (1961) A study of Adenovirus host cell system by the plaque technique *Virology 14* 234–237

Laibson P R Sery T W & Leopold I H (1963) The treatment of herpetic keratitis with 5 iodo 2 deoxyuridine (IDU) *Arch Ophthal (Chicago) 70* 52–58

Pavan Langston D & Dahlman C H (1972) A double blind clinical study of adenine therapy of viral keratoconjunctivitis *Amer J Ophthal 74* 81–88

Oxford J. S. (1976) Drug resistance and antiviral agents. *J. Antimicrobiol. Chemother.* 2, 223–224.
Underwood G. E., Elliott G. A. & Buthala D. A. (1965) *Herpes keratitis in rabbits. Pathogenesis and effect of antiviral nucleosides. Ann. N. Y. Acad. Sci.* 130, 151–167.

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OCULAR CYSTICERCOSIS

Report of a Free Floating Cysticersus in the Anterior Chamber

BY

SHASHI KAPOOR G C SOOD A L AURORA and M SOOD

A rare case of free floating cysticercus in the anterior chamber is described which mimiced a dislocated lens Preoperative use of steroids is advocated not only to controle uveitis but also facilitate surgical removal of the cyst

Key words cysticercosis – anterior chamber – cyst cysticercus – Taenia solium

The ocular involvement by the larval form of Taenia solium Cysticercus cellulosae is not infrequent The subretinal space the conjunctiva and the vitreous are the usual sites of its pathology however its occurrence in the anterior chamber is uncommon There have been very few reports available on this subject in the present and the last century (Michail 1935 Toulant 1939 Melanowski 1947 Lech 1949 Mathur & Abraham 1962 Duke Elder & Perkins 1966) The cysts whenever seen in the anterior chamber are attached to the iris the corneal back or the anterior surface of the lens (Duke Elder & Perkins 1966) Although immobile cysts are reported in the literature a freely moving cysticercus in the anterior chamber is very rare (Mathur & Abraham 1962)

The aim of the present communication is to report a rare case of free floating cysticercus in the anterior chamber which was difficult to differentiate from a dislocated lens

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Case Report

A 14 year old boy was admitted with the complaints of sudden diminution of vision in his right eye for 2 weeks

An examination of the right eye showed a mild degree of circumcorneal congestion and ciliary tenderness The cornea was hazy due to lot of keratic precipitates on its back A white spherical mass was fainty visible at 7 o clock position in the anterior chamber The pupil was small and the pattern of the iris could not be made out The visual acuity was finger counting at a distance of one meter The clinical diagnosis of uveitis due to dislocated lens was made

The patient was put on local and systemic steroids the cornea cleared up and the visual acuity improved to 6/24 after a therapy of 4 days Good details of the anterior chamber could be made out A uniformally white spherical cyst measuring 4×2.5 mm was seen fixed in the angle of the anterior chamber at 7 o clock position On its one side there was a dense white conical projection which showed undulating movements on exposure to light After a week of steroid therapy the cyst became free from its attachments and its position could be altered with a change in head posture The iris pattern was normal and there was little pigment dispersal in the anterior chamber (Fig 1)

Investigations like repeated stool and blood examination and X ray chest and skull were carried out All the investigations were negative

The cyst was removed surgically under local anaesthesia The cyst prolapsed out spontaneously as soon as the paracentasis needle was withdrawn from the

Fig 1

Photograph to show the cysticercus in the upper part of the anterior chamber

Fig 2
Photomicrograph to show cy ticercus ×400

anterior chamber Histopathological examination gave the diagnosis of cysti cercosis (Fig 2)

The final visual acuity was 6/12 at the time of discharge The eye was quiet and there was no sign of active uveitis A thorough fundus examination was carried out in the postoperative period The retina and the vitreous were found to be normal

Discussion

The human cysticercus infection is contracted by consumption of infected pork vegetables or water with the eggs of tapeworm The larval form escapes into the circulation once the envelope of the eggs is dissolved in the stomach The ocular involvement takes place through posterior ciliary arteries the larvae are deposited at places where the capillaries are narrow and the circulation sluggish Once in the eye the cyst can migrate from one part of the retina to the other (Michail 1935) and even into the anterior chamber through the pupil (Lech 1949) In our case the cyst had probably originated from the vessels feeding the ciliary body The absence of the retinal nidus the normal position of the lens little pigment dispersal in the anterior chamber and the relatively normal pattern of the iris indicate the absence of any relationship of the iris and the

retina to the origin of the cyst The original location of the cyst at ɩ o clock position i e away from the gravitational position of rest at ▮ o clock also indicates the probable origin of the cyst from the angle region

The cyst in the anterior chamber can excite uveal reaction the reaction may be so severe that it may be difficult to differentiate a cyst or a dislocated lens in the anterior chamber The history of intestinal infection may help in the diagnosis but the parasite may not be seen even on repeated stoll examination because it might have been evacuated by the time ocular involvement appears as probably ▮ the case in our patient Also the normal position and transparency of the lens help differentiating the two conditions once the inflammatory reaction subsides with steroids Steroids thus not only controle the uveal reaction but also help in loosening the attachments of the cyst by reducing exudativ▮ reaction which makes removal of the cyst an easy procedure

References

Duke Elder S & Perkins E S (1966) System of Ophthalmology Vol IX Diseases of the Uveal Tract pp 483–486 Henry Kimpton London

Lech Junior (1949) Ocular Cysticercosis *Amer J Ophthal 3⁰* 523–54ı

Mathur R N & Abraham L (196⁹) Cysticercosis of the eye *Arch Ophthal (Chica o) 6* 562–563

Melanowski W H (1949) Cysticercosis of the eye *Trans ophthal Soc U K 67* 2⁹0–239

Michail D (193ɔ) La Cysticercose Oculaire en Roumanie *Ann Oculist (Paris) I*⁹ 58ɔ–394

Toulant P (1939) Affections parasitaires de l oeil *Traite d Ophtalmologie (Paris) 8* 1 ~ı⁹2

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FACTORS AFFECTING THE SPONTANEOUS RELEASE OF [³H]GLYCINE FROM RABBIT RETINA

BY

BIRGITTA BAUER

The efflux of [^{3}H]glycine was studied in superfused rabbit retina in the presence of various amino acids ouabain or high K^+ or low Ca^{2+} concentrations in the superfusion medium Unlabelled glycine evoked an accelerated efflux as did the structurally similar neutral α amino acids β alanine and GABA were ineffective The results demonstrate a homo exchange of glycine and a heteroexchange with the neutral α amino acids A low concentration of glutamic acid (10^{-5} M) will release glycine from the retina This is an ATPase dependent process which is partially blocked by a high Mg^{2+}/Ca^{2+} ratio and which may be related to a retinal transmitter function of glutamic acid A high concentration of K^+ or the presence of ouabain in the superfusing medium greatly increases the rate at which glycine is lost from the retina

Key words retina – glycine – efflux – aminoacids – ouabain – potassium – calcium

Glycine is present in the retina as a free amino acid in concentrations ranging from 0 6 to 4 0 μmoles/g wet tissue with some species differences (see Voaden 1976) In the rabbit the concentration is 3 2 μmoles/g wet tissue Exogenously applied glycine is taken up mainly into cells which correspond in location with amacrine cells (Bruun & Ehinger 1972 1974 Marshall & Voaden 1974 Voaden et al 1974) and an active high affinity uptake mechanism has also been de

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monstrated in rabbit and frog retina (Bruun & Ehinger 1972 Voaden et al 1974) Further glycine has been shown to inhibit the firing of retinal ganglion cells (Ames & Pollen 1969) whereas the glycine receptor blocker strychnine (Curtis et al 1968) has the opposite effect (Straschill 1968) Finally light flashes release [^{3}H]glycine from the retina both *in vivo* and *in vitro* (Ehinger & Lindberg 1974 Ehinger & Lindberg Bauer 1976) Thus glycine is present in the retina affects neuronal responses can be released by stimulating the retina with its proper stimulus light and there is a reuptake mechanism that may terminate the action of released glycine This makes glycine a good candidate for being a neurotransmitter in the retina

Glycine is spontaneously released from the retina in the dark in a multiphasic pattern (Voaden 1974 Ehinger & Lindberg Bauer 1976) but factors affecting this release have not been defined In other parts of the CNS homoexchange and heteroexchange of glycine have been demonstrated for example in the spinal cord (Cutler et al 1971) and evidence has also been given for carrier mediated transport systems (Levi et al 1966) In order to better understand the release mechanisms for glycine from the retina we have studied the effect of different amino acids ions and ouabain on the efflux of [^{3}H]glycine from the rabbit retina

Material and Methods

General experimental procedure

Albino rabbits weighing about 1 5 kg were used Ten μl (10 μCi) [^{3}H]glycine were injected intravitreally into one eye after topical anaesthesia This *in vivo* labelling procedure was used in order to avoid prolonged experiments *in vitro* during which the retina might deteriorate before the experiment was finished

Two hours after the injection the rabbit was anaesthetized lightly with pento barbitone and the eye was enucleated The anterior segment and the vitreous were carefully removed The eye cup was then turned inside out and carefully placed in a specially designed water jacketed superfusion chamber (Fig 1) The everted retina was superfused at 37 C with 1 ml/min of the solution described by Ames (1965) The superfusion solution was aerated with 95 % O and 5 % CO and the experiments were run in ambient laboratory light (about 190 lux

Efflux studies

The retina was initially superfused for 30 min with Ames salt solution and for the subsequent 5–15 min with a medium containing the test substances The substances tested and their concentration in the solutions were glycine (10^{-5}

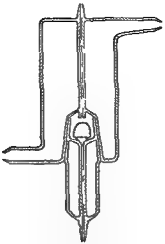

Fig 1
Schematic diagram of the water jacketed superfusion chamber The everted eye is placed on the dome shaped holder

and 10^{-4} M) β alanine (10^{-5} M and 5×10^{-5} M) α alanine (10^{-5} M) GABA (γ aminobutyric acid 5×10^{-5} M) α aminobutyric acid (10^{-5} M) L lysine (5×10^{-5} M) L leucine (10^{-5} M) valine (10^{-5} M) ouabain (10^{-4} M) K^+ (40 mM) and a Ca^{++} free medium with 2 mM EDTA

In a second series of experiments the retina was superfused as above with either the unmodified salt solution or with the latter containing 10^{-4} M ouabain or 10^{-4} M strychnine sulphate or with low Ca^{++} (0.2×10^{-3} M) and high Mg^{++} (20×10^{-3} M) concentrations The stimulation test substance (glycine 10^{-5} M or glutamic acid 10^{-5} M in the experiments with ouabain 10^{-4} M) was then applied for one min and then again for one min after 15 min

2 [^{3}H]glycine 9 4 Ci/mmole was obtained from NEN Chemicals Gmbh Dreieichenheim G F R

Analysis of superfusate

The superfusate was collected in one min samples The radioactivity of the effluent was monitored in a liquid scintillation spectrometer with quench corrections applied according to the external standard channels ratio method The absolute levels of radioactivity in the effluent at any given time will vary from experiment to experiment because the amount of label in the retina will vary from eye to eye in these *in vivo* labelling experiments The individual curves were therefore normalized so that they would always be in the same position

on the plot during the interval 25–30 min after the start of the experiment immediately before the first stimulation This normalization has applicability in all first order release processes where the release behaves as if it comes from a single compartment Expressing the amount of [^{3}H]glycine released per mg retina gives more variable results because different retinas are labelled to different degrees Also expressing release as a percentage of total radioactivity gives less precise results because more measurements and calculations are involved adding to the experimental errors As applied the normalization procedure gives a good representation of release rates However it gives no information about the absolute amounts released

Release rate constants were obtained by least squares fits of the observed efflux to the equation $y = a\ e^{-kt}$ where y is the release rate at any given time t a is the initial release rate when $t = 0$ and k is the rate constant Over 10 min intervals the fit to the equation was good with correlation coefficients of 0 95 or better Over longer periods of time (30 min or more) it was clear that the efflux has several components (Voaden 1974 Ehinger & Lindberg Bauer 19 6) and cannot be represented by the simple equation above

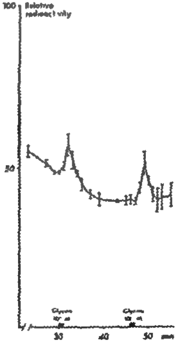

Fig 2
Effect of 10^{-5} M unlabelled glycine on the efflux ([^{3}H]glycine from rabbit retinas SEM are indicated by vertical bars 4 experiments

Since the efflux approximates a first order reaction over 10 min intervals results are directly comparable when obtained in normal retinas immediately after the normalization at a fixed time in the experimental procedure When the retinas have been pretreated for some time before normalization the efflux

Table I

Effect of different amino acids on the efflux of [^{3}H]glycine

Concentration / amino acid	5×10^{-3} M	10^{-3} M	10^{-4} M	10^{-5} M
Glycine		79 ± 15 n = 4 $P < 0\ 001$	54 ± 18 6 n = 4	27 ± 5 n = 4 1st stim. $P < 0\ 025$ 40 ± 4 6 n = 4 2nd stim $P < 0\ 01$
α alanine		30 5 ± 5 6 n = 3 $P < 0\ 05$		
β alanine	7 9 ± 1 1 n = 3 NS	5 7 ± 4 6 n = 3 NS		
α ABA				23 ± 1 6 n = 3 $P < 0\ 01$
GABA	4 4 ± 6 4 n = 4 NS			
Glutamic acid				64 ± 22 n = 5 1st stim $P < 0\ 01$ 84 ± 29 n = 5 2nd stim. $P < 0\ 01$
Leucine				21 6 ± 6 n = 3 $P < 0\ 05$
Lysine	0 9 ± 1 7 n = 4 NS			
Valine		12 1 ± 1 3 n = 4 $P < 0\ 05$		

Retinas were superfused for 30 min in normal medium to which the different substances were then added The effect is expressed as percentage increase ± SEM The statistical significance of the increase is expressed with Student's paired t test

will possibly no longer behave as if it comes from a single compartment and this restricts the interpretation of results When applicable such restrictions will be indicated in the following

The effect of stimulation is expressed as the percentage of increase of radio activity in the superfusate from the last prestimulation figure to the peak value Significances were calculated with the Student s paired two tailed *t* test

Results

Effect of glycine

The spontaneous efflux of [^{3}H]glycine was immediately increased by the addition of unlabelled glycine to the superfusion solution The effect could be demonstrated even at a low concentration (10 ^{5} M) (Fig 2) The efflux of radioactivity was accelerated by increasing the concentration of glycine in the solution (Table I) The increased release was also seen when the retina was stimu

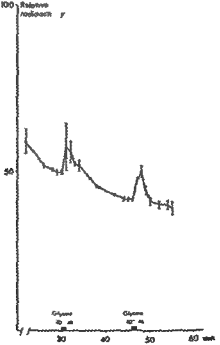

Fig 3

Effect of 10 M glycine on the efflux of [^{3}H]glycine from rabbit retinas in the presence of low Ca (0 10 ^{5} M) and high Mg + (70 x 10 ^{3} M) in the superfusion solution SEM indicated by vertical bars 4 experiments

Table II

Effect of unlabelled glycine or glutamic acid on the efflux of [^{3}H]glycine in modified superfusion solution

Stimulation substance	Modification of superfusion solution	Per cent increase of efflux ± SEM	Number of experiments
Glycine 10 5 M	0 9 mM Ca ++ 20 mM Mg +	95 ± 11 1st stim 21 ± 2 8 2nd stim	4
Glutamic acid 10- M	0 2 mM Ca ++ 20 mM Mg +	7 1 ± 4 8 1st stim 11 9 ± 5 4 2nd stim	5
Glycine 10 5 M	Strychnine – Sulphate 10-4 M	9 3 ± 4 1st stim 35 7 ± 16 3 2nd stim	4

Retinas were superfused for 30 min in the modified superfusion solution when the stimulation substance was added The effect is expressed as percentage increase ± SEM

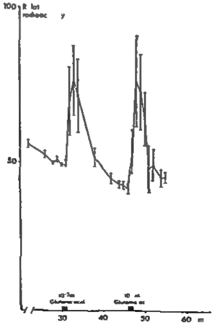

Fig 4

Effect of 10 M glutamic acid on the efflux of [^{3}H]glycine from rabbit retinas SEM are indicated by vertical bars 5 experiments

lated twice with the test solution (10^{-5} M glycine) (Fig 2) In the presence of the Na^+ K^+ ATPase inhibitor ouabain glycine (10^{-4} M) did not evoke any increased release of radioactivity Ouabain caused a significant ($P < 0.005$) change in the release rate constant from 0 0079 to 0 0323 With a low Ca and high Mg + concentration in the superfusion medium in order to suppress synaptic transmission (Masland & Ames 1976) the effect of 10^{-5} M was unchanged (Fig 3 Table II) The effect of unlabelled glycine (10^{-5} M) was not significantly decreased by strychnine sulphate (10^{-4} M) in the superfusion medium (Table II)

Effect of glutamic acid

Glutamic acid (10^{-5} M) evoked an increased release of radioactivity when added to the superfusion medium (Fig 4) This effect was significantly ($P < 0.005$) reduced with a low Ca + and high Mg + concentration in the superfusion solution (Table II) and completely abolished by 10^{-4} M ouabain (Fig 5)

Fig 5
Effect of glutamic acid (10^{-4} M) on the efflux of [^{3}H]glycine from rabbit retinas in the presence of 10^{-4} M ouabain in the superfusion solution 2 experiments

Effect of different amino acids

A summary of the results of the effect of different amino acids on the efflux of [^{3}H]glycine is given in Table I

Adding a high concentration (5×10^{-3} M) of GABA to the superfusion medium had no significant effect on the efflux of [^{3}H]glycine In contrast the analogue of GABA α aminobutyric acid even at a low concentration (10^{-5} M) increased the efflux of radioactivity significantly

β alanine (10^{-5} M or 5×10^{-3} M) had no significant effect on the efflux of [^{3}H]glycine but the analogue α alanine (10^{-5} M) stimulated the efflux of [^{3}H]glycine The neutral alpha amino acid L valine also had an accelerating effect

The large neutral amino acid L leucine stimulated the [^{3}H]glycine efflux but no effect was seen if the large basic amino acid L lysine was present in the superfusion medium even at a 5×10^{-3} M concentration

Effect of ionic alterations and metabolic inhibitions

In four experiments the normal superfusion medium was after 30 min substituted for one containing 40 mM K^+ (tonicity was maintained by a reduction in sodium ions) and a sharp rise in efflux was observed (140 % increase SEM = ± 20) When the normal superfusion medium was similarly exchanged for one containing no Ca^{++} and 2×10^{-3} M EDTA there was a prompt increase (216 % n = 2) in the release of glycine as was also the case when it was exchanged for one with 10^{-4} M ouabain (563 % n = 2)

Discussion

In efflux studies the experimental conditions should ensure a rapid removal of the released substances to reduce the possibility of reuptake Dilution should also be avoided In the superfusion technique employed in this work both the reuptake and dilution have been minimized by keeping the volume of fluid in contact with the retina at a minimum and exchanging it rapidly The retina has the advantage of being easily isolated without much damage as well as being very thin with short diffusion pathways (Ames & Nesbett 1966) Any substance released is therefore likely to appear rapidly in the superfusate This was true in the present study Furthermore intraocularly injected [^{3}H]glycine will accumulate mainly in retinal neurons and only to a very limited degree in glia so that the main part of the released radioactivity is likely to come from the neurons (Ehinger & Falck 1971 Voaden 1976)

Adding unlabelled glycine to the superfusion medium resulted in an increased efflux of [^{3}H]glycine *presumably by exchange diffusion or by competition for* its reuptake The efflux of radioactivity was accelerated by increasing the concentration of glycine in the medium in good agreement with previous results from the spinal cord (Cutler et al 1971) The effect is not caused by spreading depression because this is not readily elicited by glycine (Van Harreveld & Fifkova 1971)

Increasing the Mg^{2+}/Ca^{2+} ratio in the superfusion solution suppresses synaptic transmission (Masland & Ames 1976) When the retina was superfused in a medium with low Ca^{2+} and high Mg^{2+} concentrations no significant change in the effect of unlabelled glycine was seen suggesting that its effect is not *mediated by synaptic transmission This is further supported by the observation* that strychnine which inhibits the postsynaptic effect of glycine (Curtis et al 1968) failed to significantly depress the effect of unlabelled glycine on the efflux of [^{3}H]glycine

Glutamic acid belongs to the acidic group of amino acids Judging from the group specificity of amino acid exchange diffusion (Cratic et al 1973) no acceleration of the efflux of [^{3}H]glycine (which is a small neutral amino acid) should be expected by exposing the retina to glutamic acid However glutamic acid is known to cause cell depolarization in central neurons (Krnjević 1974) In our study on the retinas of the rabbit, unlabelled glutamic acid (10^{-3} M) *increased the efflux of* [^{3}H]*glycine as promptly as unlabelled glycine did* In contrast to the results with unlabelled glycine the effect of unlabelled glutamic acid is significantly reduced when the retina is superfused in a medium with low Ca^{2+} ($0\ 2 \times 10^{-3}$ M) and high Mg^{2+} (20×10^{-3} M) concentrations to suppress synaptic transmission The result indicates that the effect of glutamic acid on *the efflux of* [^{3}H]*glycine may be more than a heteroexchange and possibly* dependent on intact synaptic membrane mechanisms It is not likely that the effect of glutamic acid is via spreading depression because the concentration of glutamic acid is too low (20 times less than the threshold value reported by Van Harreveld & Fifkova 1971)

It would thus seem that there are receptors in the retina sensitive to glutamic acid which is what would be expected for a neurotransmitter It has previously been shown that horizontal and bipolar cells are sensitive to glutamic acid (Cervetto & MacNichol 1972 Murakami et al 1972 1975) There seems to be no direct evidence available about the sensitivity of amacrines to glutamate However both *horizontal cells and bipolar cells respond* to glutamate with sustained membrane changes whereas amacrine cells show only a transient response at the onset of the membrane changes of the bipolars If the application of glutamate does not affect the amacrine cells directly but only the bipolar

cells (and the horizontal cells) it would be expected to result in only one transient depolarization of the amacrine at the start of the application. This is hardly enough to result in the release of glycine seen in the present experiments. It is more likely that the amacrines themselves are sensitive to glutamate, responding with a release of [^{3}H]glycine.

Of the examined neutral amino acids glycine, valine, α-alanine and L-leucine all accelerated the efflux of [^{3}H]glycine, whereas β-alanine did not, even at 10^{-3} M. At a higher concentration (5×10^{-3} M) β-alanine had a slight but not significant effect. However, β-alanine has the amino group in the beta position in contrast to the other neutral amino acids which are all α-amino acids. The same was found with GABA and its analogue α-aminobutyric acid. GABA (with the amino group in the γ position) had no effect on the efflux of [^{3}H]glycine but α-aminobutyric acid had an accelerating effect even at a low concentration. The results indicate that substances accelerating the efflux of [^{3}H]glycine require an amino group in the alpha position whereas the carbon chain length is of less importance. The influence of the position of the amino group for the inhibition of the uptake of an amino acid by related amino acids has been investigated by Blasberg & Lajtha (1965). They also showed a decreasing inhibition as the amino group was positioned further away from the α-carbon.

The present demonstration that glycine may be released by a number of neutral amino acids raises the possibility that in, e.g., iontophoretic applications of such amino acids an inhibitory effect of the neuronal activity of the retina is induced indirectly by a glycine release (from neighbouring cells). Caution must be exerted so as not to misinterpret this as a direct inhibitory effect of the applied amino acid. However, such a mechanism is not possible in the retina for, e.g., GABA or β-alanine, which do not release glycine.

Upon the addition of ouabain there is a dramatic increase in the rate of release of [^{3}H]glycine from the retina. Ouabain, in inhibiting Na^+-K^+ ATPase, is known to cause an increase in the intracellular Na^+. The intracellular concentration of Na^+ may in part determine the affinity of binding of amino acids to the efflux carrier (Cutler et al. 1971). Thus the increased efflux of [^{3}H]glycine could be explained by an increased affinity of the amino acid for the efflux carrier in the presence of a higher intracellular Na^+ concentration. The increased efflux may also be an indirect effect resulting from an inhibition by ouabain of glycine uptake into the tissue. The effects of unlabelled glycine and glutamic acid were also completely abolished by ouabain, indicating that the accelerated efflux is Na^+-K^+ ATPase dependent. The results would agree with the hypothesis of Hammerstad et al. (1971) that as the carrier-mediated efflux of [^{3}H]glycine is accelerated, glycine or glutamic acid is incapable of producing any further release of [^{3}H]glycine. However, we cannot exclude

the possibility that the pretreatment with ouabain may have selectively depleted the stores from which glycine is released because the normalization procedure might also make such a depletion

Release of neurotransmitter is generally thought to occur in response to depolarization of the cell membrane Potassium in high extracellular concentration is known to depolarize the cell membrane and should thus release glycine if this is a transmitter As expected 40 mM K^+ increased the release of [^{3}H]glycine The same effect has been demonstrated on the efflux of [^{3}H]glycine from the spinal cord (Hopkin & Neal 1971) of [^{3}H]GABA from rat retina (Voaden & Starr 1972) and from brain slices (Srinivasan et al 1969)

Calcium ions are also known to play an important role in the release of neurotransmitters A Ca^{++} free medium with EDTA abolished the light induced release of [^{3}H]glycine in rabbit retina (Ehinger & Lindberg Bauer 1976 Hammerstad et al 1971) found a decrease in the electrically induced release of glycine from cat spinal cord slices under the same conditions In contrast the spontaneous efflux of [^{3}H]glycine was increased when the normal superfusion solution was exchanged for the Ca free solution with EDTA This may be the result of an increase in membrane permeability which occurs in the absence of Ca^{++} (Cutler et al 1971) or increased levels of intracellular sodium ions that also results The same effect has been noted on the efflux of glycine and GABA from rat spinal cord (Cutler et al 1971) and on the efflux of GABA and glycine from frog retina (Kennedy & Voaden 1974 Voaden 1974)

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References

Ames A (1965) Studies of morphology chemistry and function in isolated retina In Graymore W W Ed *Biochemistry of the retina* pp 22–30 Academic Press N Y London

Ames III A & Nesbett F (1966) Intracellular and extracellular compartments of mammalian central nervous tissue *J Physiol (Lond)* *184* 215–238

Ames III A & Pollen D A (1969) Neurotransmission in central nervous tissue A study of isolated rabbit retina *J Neurophysiol* *32* 424–442

Blasberg R & Lajtha A (1965) Substrate specificity of steady state amino acid transport in mouse brain slices *Arch Biochem Biophys* *112* 361–377

Bruun A & Ehinger B (1972) Uptake of the putative neurotransmitter glycine into rabbit retina *Invest Ophthal 11* 191–198

Bruun A & Ehinger B (1974) Uptake of certain possible neurotransmitters into retinal neurons of some mammals *Exp Eye Res 19* 435–447

Cervetto L & MacNichol E F (1972) Inactivation of horizontal cell in turtle retina by glutamate and aspartate *Science 178* 767–768

Cmic D M Hammerstad J P & Cutler R W (1973) Accelerated efflux of [14C] and [3H]amino acids from superfused slices of rat brain *J Neurochem 20* 203–209

Curtis D R Hosli L Johnston G A R & Johnston I H (1968) The hyperpolarization of spinal motoneurones by glycine and related amino acids *Exp Brain Res 5* 235–258

Cutler R Hammerstad J Cornick L & Murray J (1971) Efflux of amino acid neuro transmitters from rat spinal cord slices I Factors influencing the spontaneous efflux of [14C]glycine and [3H]GABA *Brain Res 35* 337–355

Ehinger B & Falck B (1971) Autoradiography of some suspected neurotransmitters substances GABA glycine glutamic acid aspartatic acid histamine dopamine and L DOPA *Brain Res 33* 157–172

Ehinger B & Lindberg B (1974) Light evoked release of glycine from the retina *Nature (Lond) 251* 727–728

Ehinger B & Lindberg Bauer B (1976) Light evoked release of glycine from cat and rabbit retina *Brain Res 113* 535–549

Hammerstad J P Murray J E & Cutler P (1971) Efflux of amino acid neuro transmitters from rat spinal cord slices II Factors influencing the electrically induced efflux of [14C]glycine and [3H]GABA *Brain Res 35* 357–367

Hopkin J & Neal M J (1971) Effect of electrical stimulation and high potassium con centrations on the efflux of [14C]glycine and slices of spinal cord *Brit J Pharmacol 4* 215–223

Kennedy A J & Voaden M (1974) Factors affecting the spontaneous release of [3H]γ aminobutyric acid from the frog retina *in vitro J Neurochem 22* 63–71

Krnjević K (1974) Chemical nature of synaptic transmission in vertebrates *Physiol Rev 54* 418–540

Levi G Blasberg R & Lajtha A (1966) Substrate specificity of cerebral amino acid Exit *in vitro Arch Biochem Biophys 114* 339–351

Marshall J & Voaden M (1974) An investigation of cells incorporating [3H]GABA and [3H]glycine in isolated retina of the rat *Exp Eye Res 18* 367–370

Masland R & Ames III A (1976) Responses to acetylcholine of ganglion cells in an isolated mammalian retina *J Neurophysiol 39* 1220–1235

Murakami M Ohtsu K & Ohtsuka T (1972) Effects of chemicals on receptors and horizontal cells in the retina *J Physiol (Lond) 227* 899–913

Murakami M Ohtsuka T & Shimazaki H (1975) Effects of aspartate and glutamate on the bipolar cells in the carp retina *Vision Res 15* 456

Shrinavasan V Neal M J & Mitchell J E (1969) The effect of electrical stimulation and high potassium concentration on the efflux of [3H]γ aminobutyric acid from brain slices *J Neurochem 16* 1235–1244

Straschill M (1968) Actions of drugs on single neurons in the cat s retina *Vision Res 8* 35–47

Van Harreveld A & Fifkova E (1971) Effects of glutamate and other amino acids on the retina *J Neurochem 18* 2145–2154

Voaden M J (1974) Light and spontaneous efflux of radioactive glycine from frog retina *Exp Eye Res* 18 46–475
Voaden M J (1976) Gamma aminobutyric acid and glycine as retinal neurotransmitters In Bonting S L Ed *Transmitters in the visual process* pp 107–125 Pergamon Press Ltd Oxford
Voaden M J Marshall J & Murani N (1974) The uptake of [3H]γ aminobutyric acid and [3H]glycine by isolated retina of the frog *Brain Res* 67 115–132
Voaden M J & Starr M (1972) The efflux of radioactive GABA from rat retina in vitro *Vision Res* 12 559–566

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TREATMENT OF KERATOCONJUNCTIVITIS SICCA WITH LIQUID PARAFFIN OR POLYVINYL ALCOHOL IN DOUBLE BLIND TRIALS

BY

M S NORN

Twenty two eyes affected with keratoconjunctivitis sicca have been subjected to double trials using the double blind randomized cross over technique
Polyvinyl alcohol in a 5 % concentration improved the condition whereas liquid paraffin aggravated it as estimated subjectively and by the measurement of the break up time of the corneal film and finally by the scoring of rose bengal vital staining of exposed cornea and conjunctiva
The conclusion is drawn *that* oil is contraindicated in keratoconjunctivitis sicca and *that* rose bengal scoring (modified Bijsterveld method) is a valuable aid in control of the sicca syndrome

Key words cornea keratoconjunctivitis sicca Sjogren s syndrome – vital staining rose bengal scoring – precorneal film break up time wetting time – polyvinyl alcohol – liquid paraffin

Keratoconjunctivitis sicca involves a reduced tear secretion reduced break up time (BUT) and vital staining of the exposed area of cornea and conjunctiva

Polyvinyl alcohol (PVA) and other viscid artificial tears improve the sicca (*Williamson et al* 1974) presumably by raising the stability of the precorneal film and reducing the outflow of tears

During treatment of normal eyes with PVA 1 4–10 % or methylcellulose 0 5–1 5 % the BUT of the precorneal film has been shown to be prolonged (Norn 1977b)

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Treatment with ointment and oil might be conceived to reduce evaporation from the precorneal film lessen the loss of fluid and thus improve the condition. However Norn & Opauszki (1977) have shown that ointment and oil cause a significant reduction of the BUT in normals

No comparisons can be made between the above investigations which were based on subjects with a normal tear secretion and patients with the sicca syndrome The latter not only have a reduced tear secretion but also have a reduced mucus flow and an increased amount of mucus (Norn 1969 1974)

It was therefore decided to carry out a double blind randomized cross over study on sicca patients using oil and PVA

Material

A total of 22 eyes (11 patients) presenting with keratoconjunctivitis sicca were examined (ten women and one man ranging in age from 42 to 76 years average age 56 8 years) Of these patients eight presented with Sjogren s syndrome.

The introductory criteria were those of typical rose bengal staining of exposed cornea and conjunctiva of pathological intensity (above 6 points out of 15 possible see method) and a pathological BUT

All except one had been treated for years with artificial tears (0 5 % methyl cellulose or 1 4 % PVA)

Method

BUT

The break up time (wetting time) was measured after instillation of 0 125 % fluorescein prior to rose bengal staining or other manipulation as described by Norn (1969 1974) The mean value of two measurements was employed

Rose bengal vital staining

Vital staining with 1 % rose bengal was quantified by a point system modified by the author after Bijsterveld (1969) The numbers of stained dots on cornea medial bulbar conjunctiva and lateral bulbar conjunctiva were estimated with the slit lamp using grades from 1 to 5 A maximum of 15 points was obtainable (5 points within each of the three controlled areas)

Table I shows the numbers of vital stained dots covering grades 1 to 5 In the presence of a few dots these could be counted directly Where the number was large counting was performed within a fairly small area (the slit lamp

Table I
Scoring of rose bengal vital staining
Number of dots counted in the following three regions cornea medial bulbar conjunctiva and lateral bulbar conjunctiva
The points are added up (maximum 15 points 6 points or less is normal)

Number of stained dots	Points
< 30	1
< 100	2
< 1000	3
< 10 000	4
> 10 000	5

light adjusted to 0 2 by 0 2 mm slit for instance) and the total number calculated At grade 5 (more than 10 000) the dots were generally confluent

Points above 6 out of a possible 15 were pathological (Bijsterveld s original method consists of a rough grading from 1 to 3 without counting (points above $3^1/_2$ out of a possible 9 are pathological))

Treatment schedule

In this randomized cross over study two pipette bottles of identical appearance were used one containing PVA in 5 % concentration the other *paraffinum liquidum tenue*

Treatment was ceased 24 h prior to initial examination After examination of BUT and rose bengal staining the patient was given a pipette bottle for instillation of drops into both eyes six times daily for 4 to 7 days

The patient was examined one or two h after the last instillation and was then given another bottle with a different content for a similar treatment

The treatment was thereafter repeated with drops from the first bottle for 4 to 7 days and then again drops from the second bottle

Statistics

After conclusion of the experiment the code was broken and the result of the double blind trial was calculated by the Wilcoxon rank sum test for pair differences

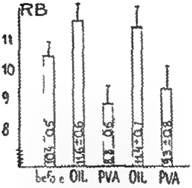

Fig 1

Treatment of keratoconjunctivitis sicca with oil (liquid paraffin) or polyvinyl alcohol (PVA) in double blind trials (?2 eyes) estimated by rose bengal vital staining (*point system maximum 15 points Values above 6 points pathological*)

Result

PVA had a better subjective effect than oil in ten patients Only one patient declared both treatments to be equally unsatisfactory

In six out of eleven patients impaired vision caused by the oil rendered reading and television difficult Four patients declared the treatment to be insupportable while six complained of swollen or red lids

Only one patient complained of sticking of the lashes after PVA 5 % whereas three patients complained of this after oil instillation

Rose bengal vital staining

The mean staining grade (± sem) is shown in Fig 1 The staining was most pronounced after treatment with oil while it was less intense though *without* reaching the normal level after PVA The starting value before treatment lay between these two grades The difference between oil and PVA is *statistically* significant (mean for oil 11 46 ± 0 46 points PVA 9 07 ± 0 48 $P < 0.01$ *in the first and in the second series*)

Mucous filaments on the cornea were most frequent in relation to oil treat*ment less so in relation to PVA treatment (50 0 % against 20 5 % P = 0 01* Wilcoxon sign test)

Fluorescein *staining was perhaps most pronounced* after oil treatment (1 91 ± 0 27 points against 1 52 ± 0 27 in the total material $P < 0.02$ in the first series *but not significant in the second series*)

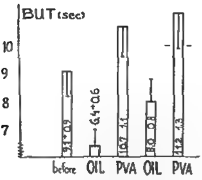

Fig 2

Treatment of keratoconjunctivitis sicca with oil (liquid paraffin) or PVA (5 % poly vinyl alcohol) in double blind trials (22 eyes) estimated by break up time (normal value $\geq$ 10 seconds)

BUT

PVA was seen to stabilize the precorneal film prolonging the BUT even up to the normal value in 55 % of the eyes (Normalized in both eyes in 3 out of 11 patients) Oil on the other hand significantly reduces the BUT (oil 7 22 $\pm$ 0 53 seconds against PVA 11 00 $\pm$ 0 86 in the total material $P < 0\ 01$ in the first series $P < 0\ 05$ in the second)

The value of BUT before treatment was found lie between that for PVA and that for oil

Comments

PVA stabilizes the precorneal film to such an extent that epithelial desiccation in sicca patients is reduced as estimated by the grading of rose bengal vital staining

Treatment with oil reduces the BUT and intensifies the vital staining This shows that neither oil nor ointment are suitable in the treatment of keratoconjunctivitis sicca

The conclusion may be drawn that oil and ointment are contraindicated in the presence of keratoconjunctivitis sicca at least during the waking hours when the patient blinks (Norn 1977a)

The fat is not sufficiently removed by the mucus transportation mechanism during blinking (cf Holly & Lemp 1977 Norn 1974) The fat appears to destroy the superficial protective layer of mucus on the epithelium

The modified Bijsterveld scoring of rose bengal vital staining seems to be a useful method of diagnosing and controlling keratoconjunctivitis sicca

References

Bijsterveld O I (1969) Diagnostic Tests in the Sicca Syndrome *Arch Ophthal (Chicago)* 82 10–14

Holly F J & Lemp M A (1977) Tear physiology and dry eyes To be published

Norn M S (1969) Mucous flow in the conjunctiva *Acta ophthal (Kbh)* 4 129–146

Norn M S (1974) External Eye Methods of Examination Scriptor Copenhagen, pp 200

Norn M S (197*a*) *Eye Ointments Application elimination and protective action Ophthalmology Digest* 39 (May) 13–18

Norn M S (1977b) Outflow of tears and its influence on tear secretion and break up time (BUT) *Acta ophthal (Kbh)* 55 674–682

Norn M S & Opauszki A (1977) Effects of ophthalmic vehicles on the stability of the precorneal film *Acta ophthal (Kbh)* 55 23–34

Williamson J Doig W M Forrester J V Tham M H Wilson T Whaley K E Dick W C (1974) Management of the dry eye in Sjogrens syndrome *Brit J Ophthal* 58 798–805

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ENDOTHELIAL CELLS IN CAPSULAR GLAUCOMA

BY

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The clinical specular microscope has made it possible to study corneal endothelial cells *in vivo* In this study we report for the first time cell den sities of unilateral glaucoma patients compared to the normotensive control eyes of the same patient.
The corneal endothelium of 27 unilateral capsular glaucoma patients was photographed with a clinical specular microscope The endothelial cell density was lower in the affected eye than in the normotensive fellow eye in 15 cases In 10 patients the cell density was the same in both eyes In two cases the glaucoma eye had a higher density than the fellow eye Comparison of the above groups showed a statistical difference in the number of glaucoma eyes with a lower cell density (15 lower against 2 higher) The endothelial cell density could not be correlated with the duration of treatment or severity of the glaucoma

Key words glaucoma capsular – pseudo exfoliation – exfoliation – fibril lopathia epitheliocapsularis – endothelial cell density – endothelial cell loss – clinical specular microscope

Slit lamp magnification is not sufficient for the study of endothelial cells Only with the specular microscope can the size morphology and quantity of endo thelial cells be examined *in vivo* (Maurice 1968 Laing et al 1975 Bourne & Kaufman 1976) The endothelial cell count of a young subject has been estab lished to be around 500 000 (3300/mm) by means of the specular microscope The number of endothelial cells decreases with age and the endothelial cell

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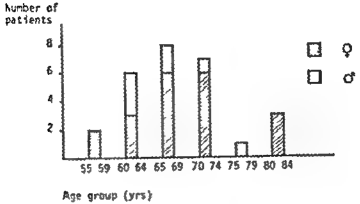

Fig 1
Age and sex distribution of patients

density of a subject aged 60 years is approximately 2600/mm (Bourne & Kaufman 1976) The endothelial cell count may also decrease after trauma when the cell regeneration capacity is either lacking or very limited (Kaufman et al 1966 Stocker 1971 Bourne & Kaufman 1976)

The purpose of this work was to study the effects of increased intraocular pressure on the endothelial cells of glaucoma patients since earlier information on the subject is very meagre In Irvine's (1956) study of enucleated glaucomatous eyes thinning of endothelial cells was demonstrated in light microscopy sections and in places the endothelium was missing

Material and Methods

The material consisted of 27 patients with uniocular capsular glaucoma which was diagnosed according to Becker & Shaffer (1976) All of them had unilateral glaucoma and a distinctly elevated intraocular pressure prior to glaucoma therapy Twenty five patients were undergoing pilocarpine treatment or other glaucoma therapy already at the time of photography Treatment was instituted after endothelial photography in two recently diagnosed cases Patients on whom an intrabulbar operation had been performed were excluded from the material because of potential surgical trauma to the endothelium The normotensive eyes of each patient constituted the control series

The intraocular pressures were measured by Goldmann's applanation tono

meter the visual fields were studied by Goldmann perimeter and the central visual field by Friedmann's analyser Tonography was performed as described by Garner (1965) by a trained person The patients ages and sex distribution are presented in Fig 1 The age range was 59–82 years Women were in the majority Fig 2 shows the duration of glaucoma treatment and presence of possible visual field defects

The endothelial cells were photographed with a specular microscope (Seyber Inc) Several pictures five on average were taken of the central cornea of both eyes of each patient The morphology and size of the endothelial cells were analysed by projecting the negative onto a screen The density of the endothelial cells was determined by counting the number visible in the specular area The magnification of the specular microscope was calculated by photographing from a standardised glass plate the calibration lines with an objective working distance which corresponds to the normal thickness of the cornea The final magnification in analysing the cells from the screen was x 730 The cells were counted from three photographs and their mean was entered as the result An area corresponding to 0 012 mm on the endothelium was calculated in each photograph and the result was expressed as the number of cells per mm

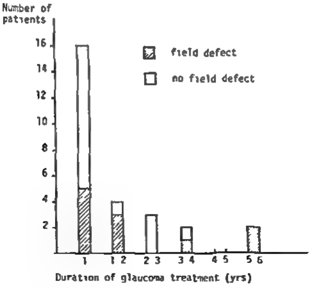

Fig 2
Visual field defects and duration of glaucoma treatment

Table I
Endothelial cell density in uniocular capsular glaucoma

Age (years)	Cell count/mm: Glaucoma eye	Cell count/mm: Healthy fellow eye	Cell count/mm: Cell diff (%)	Field defect in glaucoma eye	Duration of treatment (months)
70	2111	2467	14.4	+	18
59	2095	2369	11.5	+	12
65	2318	2608	11.1	–	12
70	2752	3064	10.8	+	6
75	21[illegible]8	2355	8.7	–	4
73	2650	2857	7.2	–	5**
60	3171	3490	7.2	–	12
59	2178	2343	7.0	+	36
61	3146	3312	5.0	–	2*
82	1[illegible]39	1822	4.6	+	12
[illegible]2	[illegible]650	2774	4.5	+	72
63	1957	20[illegible]0	4.0	–	3*
63	2525	2608	3.0	–	24
74	[illegible]494	2567	3.0	–	24
[illegible]1	2763	2818	2.4	–	3*
81	2443	2494	0	+	1
80	2[illegible]6	2542	0	+	12
[illegible]	[illegible]0[illegible]0	20[illegible]0	0	+	60
[illegible]0	[illegible]318	2318	0	–	3
69	1904	1904	0	–	36
[illegible]	2484	2484	0	–	24
[illegible]9	2194	2194	0	–	3
[illegible]9	2111	[illegible]0[illegible]0	0	–	10
[illegible]8	[illegible]484	[illegible]484	0	–	1
[illegible]	[illegible]	2[illegible]08	0	–	1
[illegible]	[illegible]05	2[illegible]4[illegible]	–5	+	3
[illegible]	[illegible]	[illegible]154	–6	+	4

** Exfoliation positive also in the normotensive fellow eye
* No treatment

A

B

Fig. 3

Large endothelial cells in glaucoma eye (Fig. 3 A) compared with the normal endothelium of the healthy fellow eye of the same patient (Fig. 3 B) × 370

Results

Endothelial cell density

We photographed with a specular microscope endothelial cells of the central cornea of both eyes of 27 patients with unilateral capsular glaucoma. We calculated the endothelial cell densities of both the glaucomatous eyes and the contralateral healthy eyes of the same patients which served as controls.

The endothelial cell density was lower in the glaucomatous than in the control eye of 15 of the 27 patients (Table I). Ten patients had the same cell count in the affected and in the control eye. There were two cases in which the cell density was lower in the normotensive than in the glaucomatous eye (3 and 6 per cent). The highest difference between the glaucomatous and control eyes was 14.4 per cent.

The mean cell count of the glaucomatous eyes was 2386/mm and of the control eyes 2516/mm. The difference was 5.2 per cent.

As the comparison was made between the eyes of the same subject personal factors affecting endothelial cell density can be disregarded Statistically 15 patients displayed a decrease in cell density in the glaucomatous eye no difference was seen in 10 cases and two eyes with glaucoma had a higher cell density than the fellow eye Although the material is fairly small the lowered cell density of 15 glaucomatous eyes and only two higher densities in the healthy eyes confirms with statistical significance the direction of the difference ($2P < 0.01$ sign test)

Correlation with the clinical picture

In seven patients exfoliation was seen also in the normotensive control eye The average cell density of the glaucoma eyes of these patients was 2361/mm and of the control eye 2470/mm The difference is 4 3 per cent

Medication had not yet been commenced in two cases at the time of photography the mean cell count of these glaucoma eyes was 2319/mm versus 2464/mm for the control eyes The difference is 5 6 per cent

Cell size and morphology varied individually Some patients displayed distinctly greater variation between the cells in the affected eyes and a couple of very large cells were even seen (Fig 3)

Comparison of the 15 cases which showed a lowered endothelial cell density with the 12 cases in which this change was not observed revealed that there was no correlation with the following parameters

- intraocular pressure on admission or a pressure difference between the affected and the control eye
- variations of the diurnal curve
- the C value or Po/C ratio
- duration of the glaucoma after admission although the pressures were highly resistant to medical treatment
- visual field defect

Discussion

The patients of our series were selected in such a way that one eye had capsular glaucoma plus elevated intraocular pressure and the fellow eye had normal pressure This made it possible to disregard individual qualities such as age etc and compare only the two eyes of the same patient The control material thus mainly differed from the investigation material only in the intraocular pressure

We observed in the cases of uniocular glaucoma a statistically significant

decrease in endothelial cell density in the glaucomatous eyes compared with the healthy fellow eyes The reason for this reduction in cell density was evidently the elevated intraocular pressure

Exfoliation and medication might be other factors reducing the endothelial cell density in our investigation material It is worthy of note that seven patients also displayed exfoliation in the control eye without elevated intra ocular pressure The cell count of the affected eyes of these patients was mostly smaller than that of the control eyes which argues against the role of exfolia tion in the lowering of the endothelial cell density Moreover it is worth stressing that no glaucoma medication had been instituted in two cases at the time of photography and yet the cell density of their glaucoma eyes was similarly lowered In addition the decrease of endothelial cell density was not correlated with the duration of glaucoma treatment (Table I) These facts do not argue for the role of glaucoma medication in the lowering of the endo thelial cell density

It seems evident that uniocular capsular glaucoma is a most suitable subject for an *in vivo* study with a specular microscope of the effects on the endothelium of long lasting intraocular pressure Interestingly our results support the con clusions made by Irvine (1956) with other methods Irvine studied 47 enucleated glaucomatous eyes and observed thinning of the endothelial cells The cell count per unit of area was generally reduced The detrimental effect of a short term increase in intraocular pressure on the endothelial cells of the cornea in animal experiments on the Vervet monkey has also been reported (Svedberg 1975) The control eye appeared morphologically normal but under higher pressure (33–44 mmHg) the eye revealed thinning of the corneal endothelial cells and changes in the ultrastructure such as vacuolisation pyknosis and exkaryocytosis

Decreasing endothelial cell density and morphological variations in the endothelial cells in the glaucomatous eye did not correlate with the duration of the glaucoma or with its signs This may be due partly to the paucity of our material and partly to still unknown factors Studies to establish the causal relationship are in progress

References

Becker B & Shaffer R N (1976) Becker Shaffer s Diagnosis and Therapy of the Glau comas 4th ed By A E Kolker and J Hetherington, Jr Mosby Saint Louis pp 220–223

Bourne W M & Kaufman H E (1976) Specular microscopy of human corneal endo thelium in vivo *Amer J Ophthal 81* 319–323

Garner L L (1965) *Tonography and the Glaucomas* Thomas Springfield Illinois
Irvine A R Jr (1956) The role of endothelium in bullous keratopathy *Arch Ophthal (Chicago)* 56 338–351
Kaufman H E Capella J A & Robbins J F (1966) The human corneal endothelium *Amer J Ophthal* 61 835–841
Laing R A Sandstrom M M & Leibowitz H M (1975) *In vivo* photomicrography of the corneal endothelium *Arch Ophthal (Chicago)* 93 143–145
Maurice D M (1968) Cellular membrane activity in the corneal endothelium of the eye *Experientia (Basel)* 24 1094–1095
Stocker F W (1971) *The Endothelium of the Cornea and Its Clinical Implications* 2nd ed Thomas Springfield Illinois pp 13–16
Svedbergh B (1975) *Effects of artificial intraocular pressure elevation on the corneal endothelium in the vervet monkey* *Acta ophthal (Kbh)* 53 839–855

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ARACHNOID CYST OF THE INTRAORBITAL PORTION OF THE OPTIC NERVE WITH UNILATERAL DISC OEDEMA AND TRANSIENT SHALLOWING OF THE ANTERIOR CHAMBER

A Case Report

BY

MATTI SAARI EILA MUSTONEN ANTTI PALVA

KALEVI JOKINEN and MAURI REUNANEN

An unusual occurrence of chronic monocular disc oedema visual loss and shallowing of the anterior chamber in a patient with an arachnoid cyst involving a portion of the intraorbital optic nerve was reported Decompression of the optic nerve sheath through a Kronlein approach was followed by prompt deepening of the anterior chamber and a gradual delayed relief of the disc oedema It is concluded that orbitotomy and decompression of the optic nerve sheath should be done before atrophic changes of the optic nerve and visual loss begin to develop

Key words arachnoid cyst – depth of anterior chamber – optic disc – optic nerve – orbitotomy – papilloedema – surgery

Unilateral optic disc oedema may be caused by a cyst of the intracranial (Holt 1966) or intraorbital (Smith et al 1969 Miller & Green 1975) portion of the optic nerve sheath We describe a patient with chronic unilateral optic disc oedema visual loss shallowing of the anterior chamber and optociliary veins due to a cyst involving a portion of the intraorbital optic nerve

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Case Report

A 29 year old woman complained of slight pain on eye movements and transient attacks of blurred vision in the left eye for 2 weeks prior to admission to the eye department on Jan 30 1975 Visual acuity was 1 3 and refraction +0 25 D sph ⊂ +0 75 D cyl ax 90 in both eyes The right eye was normal A fulminant optic disc oedema with blurred disc margins and small linear haemorrhages was seen in the left eye (Fig 1) Vasodilatation increase in the number of visible capillaries microaneurysms and fluorescein leakage were seen on fluorescein angiography of the left optic disc (Fig 2) Hertel measurements were 15 mm bilaterally with a base of 95 mm Extraocular movements were full with a 4 prism dioptre exophoria General physical and neurological examination revealed nothing abnormal Skull orbit and optic canal X ray films orbital venogram left carotid arteriogram brain scan echo encephalogram and electroencephalogram revealed normal findings At lumbar puncture the spinal fluid pressure was 1_0 mm of water

In the course of one month in spite of continued prednisone therapy the patient developed a gradual loss of vision to 0.5 increase in the disc oedema to the macular area with development of a macular star figure and pronounced enlargement of the blind spot Progressive optic disc oedema and visual loss without proptosis and normal results of studies for intra cranial or intra orbital pathologic findings made neurosurgeons suggest a transfrontal craniotomy and exploration of the optic canal for a suspected intracanalicular meningioma of the optic nerve sheath

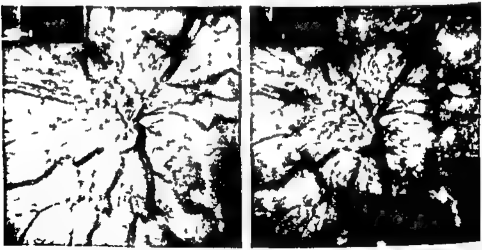

Fig 1

Stereophotographs *showing fulminant optic disc oedema* Photographs can be viewed by placing a 5 sphere before both eyes and viewed from a distance of 20 cm To avoid converging on the photograph a sheet of paper can be placed at the junction of the two photographs and extending up to the nose

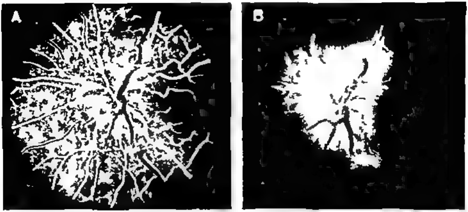

Fig 2

A Fluorescein angiogram in early venous phase showing dilatation of capillaries on the oedematous optic disc

B Diffuse fluorescein leakage in late phase

On admission to the Department of Neurosurgery University of Helsinki on March 20 1975 the visual acuity in the left eye was 0 1 There was an afferent pupillary defect on the left Pneumoencephalogram was normal On March 27 1975 a left side frontal craniotomy and exploration of the optic canal revealed nothing abnormal Unroofing of the left orbit was not performed

On admission to the University Eye Hospital in Oulu on April 2 1975 the left vision was counting fingers at 60 cm. The refraction was +2 75 dioptres By applanation

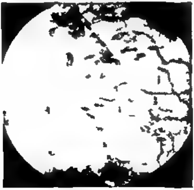

Fig 3

Extreme degrees of oedema haemorrhages and exudates on the optic disc and in the macular area

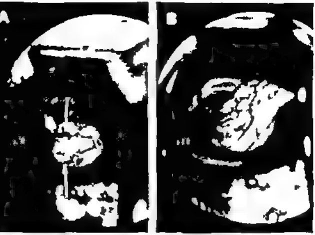

Fig. 4

A. Cyst of optic nerve sheath (thin arrows) posteriorly to the globe (thick arrow).

B. Optic nerve (arrow) and collapsed nerve sheath are seen after decompression.

tonometry intraocular pressure was 14 mmHg in both eyes. The anterior chamber was 3.8 mm deep in the right eye and 2.1 mm deep in the left measured with Haag-Streit instruments. We graded the chamber angles as grades 4 (open) in the right eye and as grades 0–1 and 1–2 (narrow) in the left eye in gonioscopy. The left optic disc was swollen 5 dioptres as measured by ophthalmoscopy. On April 5, 1975, visual acuity was CF 20–30 cm and refraction +7.75 D sph $\bigcirc$ +0.5 D cyl ax 90° in the left eye. On April 14 the left vision was hand movements in superior and nasal quadrants. There was considerable oedema, haemorrhages, exudates and neovascularisation on the optic disc, the borders of which were not discernible (Fig. 3). Oedema and haemorrhages were seen in the macular area.

On April 16, 1975 the left orbit was explored under general anaesthesia. The lateral wall was removed by means of the Krönlein approach. The optic nerve was exposed and was noted to be 11 mm in thickness beginning posteriorly to the globe and extending for a length of 8 mm (Fig. 4). The nerve sheath was incised in this area. A moderate amount of clear yellowish fluid was seen to escape immediately. From the superior edge of the collapsed nerve sheath a small portion (1.5 by 4 mm) was excised for histologic study and for decompression of the perineural space (Fig. 4). Histopathologic examination of the biopsy specimen showed no evidence of tumour or inflammation and was reported as a normal optic nerve sheath.

Healing of the wound was prompt. After three days anterior chamber was 2.5 mm deep bilaterally. The disc swelling resolved markedly during the first five days but thereafter slowly. The vision did not return. Nine months later the left eye was blind, the disc margins were well defined and the disc was atrophied showing optociliary shunt vessels on its superior and inferior borders (Fig. 5).

Fig 5
Atrophic optic disc with optociliary shunt vessels (arrows)

Discussion

The subdural space surrounding the optic nerve is dilated close to the eye in most cases of papilloedema occurring usually bilaterally (Walsh & Hoyt 1969) In this case however the intracranial pressure was normal and the patient had unilateral optic disc oedema without proptosis The optic foramen and the intracranial portion of the left optic nerve as well as the left orbit were explored and nothing abnormal was seen with the exception of the cyst of the optic nerve sheath

Increased intravaginal pressure is an essential element in the production of papilloedema (Hayreh 1964) At operation the optic nerve sheath was dilated and firm and when an incision was made into the sheath a stream of clear fluid escaped with such a force as to imply that considerable pressure must have been present within the cyst Incision of the cyst of the nerve sheath diminished the optic disc oedema and eliminated occurrence of transient shallowing of the anterior chamber Thus there can be no doubt that the lesion enlarging the optic nerve sheath was the cause of the chronic papilloedema in this patient

Surgical decompression of the optic nerve sheath allows simultaneous orbital exploration biopsy and effective treatment for chronic unilateral optic disc oedema To improve the patient s visual prognosis decompression of the peri optic meninges should be done before atrophic changes of the optic nerve and visual loss begin to develop

Frisén et al (1973) reported optociliary veins disc pallor and visual loss as

a triad of signs indicating spheno orbital meningioma Similar signs were seen in our patient with a cyst of the optic nerve sheath as well as in a similar patient reported by Miller & Green (1975) We agree with Miller & Green (1975) that the triad of optociliary veins disc pallor and visual loss may also occur in other indolent tumours of the perioptic meninges besides meningioma

Grant (19 3) reported shallowing of the anterior chamber following occlusion of the central retinal vein Our patient with severe disc oedema revealed shallowing of the anterior chamber obviously due to an increase of volume within the posterior segment This is the first reported case with arachnoid cyst of the optic nerve and transient shallowing of the anterior chamber The anterior chamber deepened within 3 days of the decompression of the optic nerve sheath presumably due to resorption of blood and oedema fluid from the optic disc and retina

Acknowledgment

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References

Frisén L Hoyt W F & Tengroth B M (19.3) Optociliary veins disc pallor and visual loss A triad of signs indicating spheno orbital meningioma *Acta ophth (Kbh)* 51 241–249

Grant W M (19 3) Shallowing of the anterior chamber following occlusion of the central retinal vein *Amer J Ophthal* 75 334–339

Hayreh S S (1964) Pathogenesis of oedema of the optic disc (papilloedema) A preliminary report *Brit J Ophthal* 48 522–543

H h H (196) Cysts of the intracranial portion of the optic nerve *Amer J Ophthal* 1 1106–11 0

Miller N R & Green W R (19 5) Arachnoid cysts involving a portion of the intraorbital optic nerve *Arch Ophthal (Chicago)* 93 1117–1121

Smith J L Hoyt W F & Newton T H (1969) Optic nerve sheath decompression for relief of chronic monocular choked disc *Amer J Ophthal* 68 633–637

Walsh F B & Hoyt W F (1969) *Clinical neuro-ophthalmology* p 63 Vol 1 3rd ed Williams & Wilkins Co Baltimore

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THE CILIARY BODY AND THE SUSPENSION OF THE LENS IN A MONKEY (CERCOPITHECUS AETHIOPS)

A Scanning Electron Microscopic Study

BY

MARTIN DAVANGER and AMUND RINGVOLD*

The zonules of Zinn and their insertion on the ciliary body and the lens in a monkey (Cercopithecus aethiops) have been studied with the scanning electron microscope The specimens were dissected after drying by the critical point method and the lens was separated from the ciliary body by simple traction The pars plana was completely covered by a mat which consisted of meridionally directed zonule like fibers Most of these fibers inserted at the base of the posterior end of the ciliary processes and some of them radiated into the valleys between the processes About two fibers for each process split off from the mat and became attached to the sides of the processes near their posterior ends The true zonules spanned from the sides of the processes to the pre and post equatorial region of the lens They were clearly separated into an anterior and a posterior row with no fibers crossing over from one row to the other Usually four true zonules joined each process i e one zonule of the anterior row and one of the posterior row attached to each side of the single ciliary process

Key words zonules of Zinn – lens – ciliary body – accommodation – primate – scanning electron microscopy

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The zonules of Zinn have commonly been described as arising from the region of the ora serrata and the pars plana ciliaris. From here they have been said *to course forward along the concavity* of the *pars plana passing through* the valleys between the ciliary processes before they insert on the equatorial region of the lens. Some additional fibers have also been observed originating from the valleys between the processes. In total the fiber arrangement shows a criss-cross pattern through some units crossing the main direction before the insertion on the pre- or postequatorial lens region (McCullock 1954, Vail 195-, Wolff 1961, Bornfeld et al. 1974).

Recent scanning electron microscopic studies of human eyes revealed observations concerning the lens suspension which differed from the view previously held. *The zonule-like fibers covering the pars plana do not pass on to the lens* but insert on the posterior part of the ciliary processes. Other fibers arising from the anterior part of the processes bridged directly *onto the* equatorial region of the lens (Davanger 1975a). Some light microscopic evidence supporting this interpretation has been presented (Moses 1975).

In the present study anatomical details of the lens suspension have been examined in a monkey (Cercopithecus aethiops) commonly used in eye research. The technique of preparation of the specimens has been somewhat altered and refined as compared to earlier studies. New details of the course and insertions of the zonules will be described.

Material and Methods

One eye from each of three vervets (Cercopithecus aethiops) weighing between 4.? and 4.9 kg were used. Anaesthesia was performed with an intramuscular injection of 50 mg methohexital sodium (Brietal) followed by an adequate dose of mebamal sodium (60 mg/ml) intravenously, starting with 0.5 ml. In order to obtain optimal preservation of the *in situ* relations of zonules, lens, and ciliary body, the anterior chamber was perfused with 1.5% glutaraldehyde 0.1 M sodium cacodylate (pH 7.3) at about 2? mmHg (the eyes were additionally planned for a different purpose, hence this slightly elevated pressure). Push-pull coupled syringes were applied so that the aqueous humour was replaced with glutaraldehyde solution immediately after starting fixation without changing the intraocular pressure. After 15-20 min the anterior chamber perfusion was stopped, the thorax was opened, and fixation was continued with 4% paraformaldehyde sodium phosphate *buffer with 5% sucrose* (pH 7.4) perfused through the left ventricle after having rinsed the vessels shortly with buffer only. Subsequently the anterior eye segment was cut off at equator level, divided into four sectors and put into 1.5% glutaraldehyde 0.1 M sodium cacodylate for another 1½ h. The tissue was then thoroughly rinsed in cacodylate buffer, postfixed for 3 h in 1% OsO_4 0.1 M sodium cacodylate, pH 7.?, and kept in the buffer overnight.

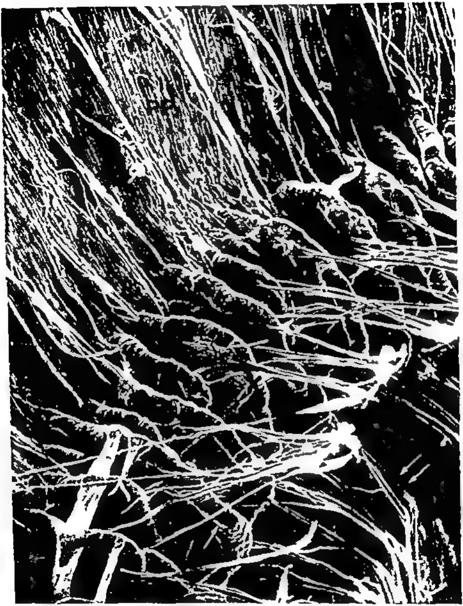

Fig. 1
The ciliary body with the pars plana (PP) the ciliary processes and the zonules A mat of zonule like fibers covers the pars plana Some fibers are lifted up from this mat The zonules are separated in a posterior row (arrow) and an anterior row (double arrow) ×78 Bar = 0 1 mm

After dehydration in graded acetone solutions the specimens were dried in fluid CO at the critical point (Sorwall Critical point drying system) The vitreous remnants were then carefully removed from behind under the operating microscope Except for the most peripheral part of the pars plana the dried vitreous loosened from the lens zonules and the ciliary processes without causing obvious damage to these structures At this stage the lens and the ciliary body were separated by simple traction whereby the zonules became loosened at their attachment to the lens in some sectors in other sectors they broke close to their insertion into the ciliary processes The specimens were mounted on specimen holders and coated with a thin layer of carbon and gold palladium in an Edward s vacuum coating unit Jeol JMS 50 SEM was used for this microscopy In addition some specimens were processed for transmission electron microscopy and examined in a Philips EM 400

Fig °

The anterior part of the mat of fibers covering the pars plana and the posterior ends of the ciliary processes Zonule like fibers above the mat attach to each side of the processes at their posterior ends 2 0 Bar = 50 μm

Fig 3

Part of an epithelial cell (E) of the pars plana with the internal limiting membrane (arrow) and part of a fiber (z) of the mat covering the pars plana An empty space separates the fiber from the internal limiting membrane Araldite embedded Uranyl acetate/lead *citrate staining Transmission electron microscopy x 39 000 Bar = 1 μm*

Results

The pars plana was completely covered by meridionally directed zonule like fibers forming a tight mat along its concave surface The fibers attached posteriorly in the region of ora serrata Anteriorly most of them inserted at the base of the posterior ends of the ciliary processes whereas some inserted in the valleys between the processes (Fig 1) The majority of the fibers remained integrated in the mat for their whole length However a few of them about two for each process split off from the mat and took a course above its inner surface These fibers inserted on the posterior region of the ciliary processes one on each side of them clearly above the surface of the mat (Fig 2) This

Fig 1

The ciliary processes with the zonules which are clearly separated in an anterior row (arrow) and a posterior row (double arrow) In the background in upper left corner the iris (i) is seen and in lower right corner the mat on the pars plana (PP) ×95 Bar = 0 1 mm

Fig 5

The mat of fibers covering the pars plana (left side) the fibers lifted up from this mat (arrow) the zonules of the posterior row (right side) with their fan shaped insertion on the sides of the ciliary processes × 125 Bar = 0 1 mm

insertion defines these fibers and demonstrates that they are separate units which differ from the majority of the fibers constituting the mat These fibers adhered to the anterior vitreous surface at least in the dried specimens and their course (but not their attachment) may have been somewhat altered during the removal of the vitreous

The mat of fibers was easily separated from the true surface of pars plana by dissection The epithelial surface uncovered by this procedure had a cobble stone like surface as each single cell was protruding and demarcated from neighbouring cells The relationship between the epithelial layer and the mat of fibers was elucidated by sections which showed that these structures were separated by an empty space over wide areas (Fig 3) The internal limiting membrane was intact in these regions and only here and there did bundles of fibrils split off from the mat to become attached to the cell layer

The zonules *sensu strictiori* bridged the space between the ciliary processes and the lens by a direct course They were clearly separated into an anterior and a posterior row each row inserting into the pre and post equatorial lens region respectively While the zonules within each row roughly ran in parallel the zonules of the anterior and the posterior row were markedly diverging from each other in their course (Fig 4) Fibers crossing over from the anterior to the posterior row and *vice versa* were not observed

The zonules of the posterior row were mainly attached to the sides of the ciliary processes and they inserted on the middle of the processes near their ridges (Fig 5) Each zonule divided into several subunits forming a fan like pattern on the process side roughly following the same course as the zonule itself i e towards the posterior part of the valley between the processes Some of the fan subunits continued into the mat fibers of the pars plana or into th subunits formed at the insertion of those fibers which were lifted up from this mat It should be stressed however *that onules directly connecting the lens*

Fig 6
The equatorial region of the lens with the insertion of the zonules Some zonules have been torn away during the preparation × 120 Bar = 0 1 mm

Fig ,

The equatorial region of the lens The anterior and the posterior row of zonules with their attachment to the lens ×135 Bar = 0 1 mm

and the pars plana were not seen The zonules of the anterior row attached to the process sides near their anterior regions through fan insertions similar to that described for the posterior zonules

Usually at least one zonule in the posterior row and one in the anterior row were attached to each side of the ciliary process i e at least four true zonules joined each process (Fig 1) Since thin irregularly coursing fibers frequently occurred many processes were attached by more than four true zonules

As the lens was pulled away from the rest of the dried specimen the zonules were usually detached at their insertions on the lens surface The zonules thus remaining attached to the ciliary body ended as flat fans without any supporting structure (Figs 1 and 4) In some locations however the zonules were broken near the ciliary body and many of these remained intact along the lens surface (Fig 6) At the site of insertion the zonules spread into subunits forming fans attached to the lens capsule (Fig 7) as previously described in human eyes (Davanger 1975a)

Discussion

The critical point drying procedure used in the present study is preferable to the method used by Davanger (1975a) as the possibility of introducing artifacts is supposed to be reduced by this method Drying by critical point does not result in obvious uneven shrinkage and folding of the specimen and surface details are preserved better The removal of the lens in the dried specimen made it possible to look at the ciliary body and the zonules from different angles and the procedure did not change the course of the zonules In addition the *in situ* fixation gives optimal preservation of the spatial relations between the different structures

As shown in the present paper the lens suspension of the vervet monkey is principally similar to earlier observations in human eyes (Davanger 1975a) The fibrils crossing the main fiber direction on the pars plana described by Davanger (1975a) were found neither in a later study of human eyes (Davanger 1975b) nor in the present work These crossing fibers may be artifacts

The tight fibrous mat covering the inner surface of the pars plana both in man (Davanger 1975a Moses 1975) and in monkey was not found by scanning electron microscopy of rabbit eyes (unpublished observation) These fibers probably exert a stabilizing function on the ciliary processes as they in part counteract the zonular pull on these structures from the lens Since the range of accommodation is small in rabbit compared to man and monkey (Prince 1964) there is obviously no need for any fibers to anchor the ciliary processes towards the pars plana in this species

References

Bornfeld N Spitznas M Breipohl W & Bijvank G J (1974) Scanning electron microscopy of the zonule of Zinn I Human Eyes *Albrecht v Graefes Arch klin exp Ophthal 19[illegible]* 117–129

Davanger M (1975a) The suspensory apparatus of the lens The surface of the ciliary body A scanning electron microscopic study *Acta ophthal (Kbh) 53* 19–33

Davanger M (1975b) The pseudo exfoliation syndrome A scanning electron microscopic study II The posterior chamber region *Acta ophthal (Kbh) 53* 8[illegible]1–833

McCullock C (1954) The zonule of Zinn Its origin course and insertion and its relation to neighboring structures *Trans amer ophthal Soc* [illegible] 5[illegible]–585

Moses R A (1975) In *Adler s Physiology of the eye* Moses R A Ed pp 303–311 The C V Mosby Company St Louis USA

Prince J H (1964) In *The rabbit in eye research* Prince J H Ed pp XII–XIII Charles C Thomas Publisher Springfield USA

Vail D (1957) The zonule of Zinn and ligament of Wieger *Trans ophthal Soc U K* *77* 441–499
Wolff E (1961) In *Anatomy of the eye and orbit* fifth ed revised by R J Last H K Lewis & Co Ltd London

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THE EFFECT OF POLYPHLORETIN PHOSPHATE ON THE AQUEOUS FLARE RESPONSE TO α MELANOCYTE STIMULATING HORMONE

BY

ELISABETH BENGTSSON

The breakdown of the blood aqueous barrier caused by topical prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2) or subcutaneous α melanocyte stimulating hormone (α MSH) was quantified by measurements of the aqueous flare seen in the anterior chamber. Polyphloretin phosphate (PPP) administered subcutaneously was found to effectively block the protein leakage caused by all three traumatic stimuli. The same dose of PPP given intravenously inhibited effectively the flare response to PGE_1 and α MSH whereas the effect of PGE_2 was only slightly decreased.
Significant inhibition by subconjunctival PPP was not achieved for any of the three stimuli.
Assuming that PPP is a specific PG antagonist the present results support the earlier suggestion that PGs take part in the barrier damaging action of α MSH. However, it cannot be excluded that PPP acts on a step subsequent to PG. This step might be common to PGs and α MSH effects on the barrier, explaining why PPP inhibits both types of trauma.

Key words: blood aqueous barrier – aqueous flare – prostaglandins – α melanocyte stimulating hormone – polyphloretin phosphate

Indomethacin and acetyl salicylic acid – inhibitors of prostaglandin synthesis (Vane 1971) – fail to prevent the breakdown of the blood aqueous barrier seen in rabbit eyes after subcutaneous injection of α melanocyte stimulating hormone

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(α MSH) (Neufeld et al 1972 Bengtsson 1975) Thus it appears as if the mechanism of the α MSH effect is different from most other traumatic agents to the eye which exert their effect via enhanced prostaglandin (PG) synthesis (Neufeld et al 1972)

The barrier damaging effect of α MSH (Bengtsson 1976) as well as of PG mediated stimuli (Bengtsson 1976 Zink et al 1973) could however be abolished by intraperitoneal imidazole indicating that the ultimate barrier disturbing mechanism might anyhow be the same for different types of traumata Adenosine 3 5 cyclic monophosphate (cAMP) has been proposed to be this common link (Zink et al 1973 Waitzman & Woods 1971) and imidazole has been thought to exert its inhibiting effect by stimulating the inactivation of cAMP (Butcher & Sutherland 1962) However imidazole administered topically instead of intraperitoneally strongly facilitated and potentiated the α MSH response while there was no effect on PG mediated stimuli (Bengtsson 1976) In a recent study α MSH was found effectively to increase the PG accumulating capacity of the iris ciliary body (Bengtsson & Ehinger 1977) This study also indicated that topical imidazole facilitates and potentiates the protein leakage after α MSH by further promoting the increase of PG accumulation caused by α MSH Thus it seems as if PGs might somehow take part in the disruption of the blood aqueous barrier after subcutaneous α MSH though not by enhanced PG synthesis

To investigate whether prostaglandins actually contribute in some way to the barrier damaging activity of α MSH we wanted to test whether an agent possessing prostaglandin antagonistic actions could also prevent the α MSH effects Polyphloretin phosphate (PPP) has long been known as an inhibitor of a variety of enzymes and of prostaglandins Beitch & Eakins (1969) first demonstrated that PPP prevented the breakdown of the blood aqueous barrier and increase in intraocular pressure produced by PGE_2 injected into the rabbit eye In subsequent studies PPP was shown to be a selective antagonist of prostaglandin actions on the isolated gerbil colon (Eakins et al 1970)

To test the hypothesis mentioned above the present study investigated whether the barrier damaging action of α MSH in rabbit eyes could be inhibited by pretreatment with the prostaglandin antagonist PPP

Material and Methods

Animals Adult pigmented rabbits (1 8–2 2 kg) of mixed strains were used They were given pellets and water ad libitum

Chemical preparations Prostaglandin E_1 (PGE_1) (Upjohn Co Kalamazoo Michigan) and prostaglandin E (PGE) (Upjohn Co) were dissolved in 0 9 % saline giving a solution containing 0 5 mg ml^{-1} and stored at −95°C α MSH (CIBA Basel Schweiz) was freshly dissolved in 0 9 % saline (100 μg ml^{-1})

Polyphloretin phosphate (PPP) (Leo Laboratories Helsingborg Sweden) and diphloretin phosphate (DPP) (Leo Laboratories Helsingborg Sweden) were freshly dissolved in 0 9 % saline to a concentration of 100 mg ml^{-1} and 50 mg ml^{-1} respectively

Aqueous flare response The course of the protein leakage into the anterior chamber – reflecting the barrier damage caused by the different traumatic stimuli – was followed by quantitative measurements of the aqueous flare by use of a previously described photoelectric instrument (Technical note in Bengtsson 1975) The measurements were undertaken on the intact eye and no anaesthesia was needed The flare was measured in arbitrary units

Statistics Wilcoxon's test for paired differences was used for calculating the significance of differences *P* refers to the null hypothesis (H_0)

Table 1

The *testing of the effect of polyphloretin phosphate (PPP) on* the breakdown of the blood aqueous barrier in the rabbit eye induced by topical prostaglandin E (PGE) topical prostaglandin E_1 (PGE_1) or subcutaneous α melanocyte stimulating hormone was performed according to this scheme

PPP	Interval min	Stimuli	No of rabbits
0 1 ml 10 % PPP given subconjunctivally to the right eye	30	2 5 μg PGE both eyes	7
	30	1 5 μg PGE_1 both eyes	5
	[illegible]	α MSH sc (20 μg/kg bodyweight)	5
900 mg PPP given intravenously over a 5 min period	15	2 5 μg PGE one eye	[illegible]
	15	1 5 μg PGE_1 one eye	8
	0	α MSH sc (90 μg/kg bodyweight)	8**
700 mg PPP given subcutaneously	30	2 5 μg PGE one eye	8
	30	1 5 μg PGE_1 one eye	9
	0	α MSH sc (20 μg/kg bodyweight)	8**

* The left eye was used as control eye

** Selected group of animals with an extremely strong aqueous flare response to α MSH

Experiments

A breakdown of the blood aqueous barrier was elicited by topical application onto the cornea of 2 5 μg PGE$_2$ or 1 5 μg PGE$_1$ or by subcutaneous (sc) injection of 20 μg/kg bodyweight α MSH The aqueous flare was measured every half hour until the maximum flare response was covered or if no increase occurred for four to five hours following stimulation The testing of the effect of PPP on the aqueous flare response to the traumatic stimuli was performed according to the scheme shown in Table I As a control the irritative stimuli were administered to the same groups of rabbits about 14 days before or after the event at which the effect of intravenous or subcutaneous PPP had been tested For PGE$_1$ and PGE$_2$ the contralateral eye was used for this control

In one group of rabbits (5 animals) it was tested as to whether 100 μl 10 % PPP given topically every ten min during the hour prior to topical administration of 2 5 μg PGE$_2$ affected the protein leakage

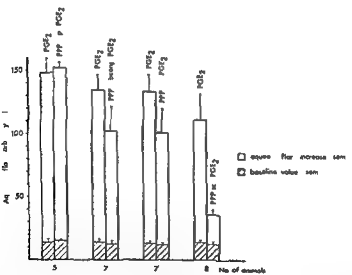

Fig 1

Aqueous flare response to 2.5 μg prostaglandin E (PGE$_2$) given topically after prior treatment with

a) 100 μl of 10 % polyphloretin phosphate (PPP) given topically six times with ten min interval
b) 0 1 ml of 10 % PPP injected subconjunctivally 30 min earlier
c) ?00 mg PP given intravenously 15 min earlier
d) 200 mg PPP given subcutaneously 30 min earlier

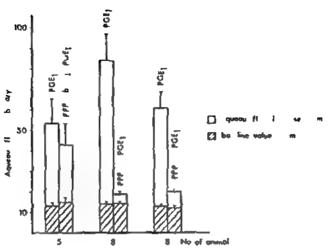

Fig 2

Aqueous flare response to 1 5 μg PGE_1 given topically after prior treatment with

a) 0 1 ml 10 % polyphloretin phosphate (PPP) injected subconjunctivally 30 min earlier
b) ?00 mg PPP given intravenously 15 min earlier
c) ?00 mg PPP given subcutaneously 30 min earlier

In another group of rabbits (5 animals) it was tested as to whether 0 1 ml DPP (50 mg ml⁻¹) given subconjunctivally inhibited the aqueous flare response to 1 5 μg PGE_1

As a control the aqueous flare was followed in groups of rabbits (5–8 rabbits in each) which had been treated with PPP or DPP administered as in our different test groups and in one group of animals (6 rabbits) 0 1 ml 0 9 % saline was injected subconjunctivally

Results

Subconjunctival PPP The aqueous flare response to topical PGE (Fig 1) and to topical PGE_1 (Fig 2) was slightly decreased by subconjunctival PPP This decrease was however not significant The effect of α MSH was not changed at all (H_0 $P > 0.10$) by PPP given subconjunctivally (Fig 3) However in 25 % of the total amount of subconjunctivally injected eyes a pathological aqueous flare increase appeared within 30 min of the injection so these rabbits must be excluded from the test series To be quite sure that a traumatic reaction caused by subconjunctival PPP did not interfere with the flare response to the irritative stimuli animals in which an aqueous flare response was registered

within 15 min of the prostaglandin application or 30 min of the α MSH injection were not accepted either Allowance being made for these exclusions no effect of subconjunctival PPP on the time relationships of the inflammatory course was recorded in any experiment In those rabbits (8 out of 31 animals) in which subconjunctival PPP per se caused a barrier damage the aqueous flare always started to rise within 30 min and the maximal flare increase was reached after about one and a half hours In the control group consisting of 8 animals in which one eye was given PPP subconjunctivally no flare increase at all was recorded in 6 animals

After subconjunctival injection of PPP a local conjunctival swelling and vasodilation could be seen for about 5–6 hours following the injection even in those eyes in which no protein leakage could be recorded

0 1 ml 0 9 % saline administered subconjunctivally did in no case cause any protein leakage and all external signs of the injection had vanished after about one hour

Intravenous PPP The barrier damage caused by topical PGE was only slightly (H_0 $P > 0\ 10$) decreased by intravenous PPP (Fig 1) The PGE_1 (Fig 2) and the α MSH response (Fig 3) were however markedly inhibited (H_1 $P < 0\ 01$)

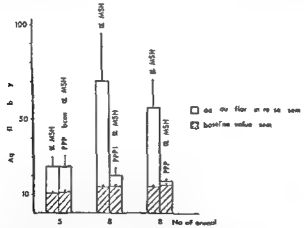

Fig 3

Aqueous flare response to 90 μg/kg bodyweight α melanocyte stimulating hormone (α MSH) given subcutaneously at the same time as

a) 0 1 ml 10 % polyphloretin phosphate (PPP) injected subconjunctivally
b) 200 mg PPP given intravenously
c) 200 mg PPP given subcutaneously

Selected group of animals with an extremely strong aqueous flare response to α MSH

by pretreatment with intravenous PPP The time relationships of the inflammatory course were not altered for any of the three stimuli Intravenous PPP per se did not affect the physiological aqueous flare

Subcutaneous PPP PPP given subcutaneously significantly decreased (H_0 $P < 0\ 01$) the aqueous flare response to PGE (Fig 1) PGE_1 (Fig 2) and α MSH (Fig 3) Subcutaneous PPP did not change the time relationships of the response to the irritative stimuli nor did it affect the physiological aqueous flare

Topical PPP Topical PPP had no effect (H_0 $P > 0\ 10$) on the protein leakage caused by PGE (Fig 1)

Subconjunctival DPP When DPP had been given subconjunctivally 30 minutes before the application of *1 5 μg* PGE_1 *topically* the mean of the maximal aqueous flare response was 55 0 ± 8 9 arbitrary units whereas the response to merely PGE_1 *was 56 8 ± 10 arbitrary units Thus no effect of subconjunctival* DPP on the barrier damage after PGE_1 could be recorded Subconjunctival injection of DPP caused local irritation and protein leakage to about the same extent as seen after subconjunctival PPP

Discussion

Whitelocke & Eakins (1973) have demonstrated that the vasodilatation and the increased permeability to fluorescein of the vessels in the anterior iridial surface caused by 25 μg topical PGE_1 or PGE could be prevented by pretreatment with subconjunctival PPP The effects of 25 μg topical PGEs on the base of the iris (reflecting the reactions of the ciliary region) was however not affected by subconjunctival PPP Moreover when PGF (200 μg) or smaller doses (6 μg) of PGE_1 or PGE were applied topically there were detectable effects only in the basal part of the iris nor could these effects be inhibited by subconjunctival PPP whereas the rise in intraocular pressure produced by all three PGs was effectively blocked Their study indicates that PPP has inhibiting effects on PGs but it also shows that the subconjunctival route of administration of PPP is not an effective one for significant effect on the PG actions in the ciliary region This is in accordance with the present study in which we could not demonstrate any marked effect on the protein leakage caused by the damaging effect of PGs (1 5–2 5 μg) or α MSH on the blood aqueous barrier in the ciliary region On the contrary we had problems in avoiding a barrier breakdown by the subconjunctival injection of PPP per se

The present results also agree with a study (Kelly & Starr 1971) on monkey eyes in which it was found that intracameral PPP did not inhibit the protein leakage produced by PGs although the rise in intraocular pressure was prevented by PPP It seems as if the intraocular pressure increase caused by PGs and traumatic stimuli is more easily counteracted by PPP than is the aqueous flare response This may explain the discrepancy between the poor PG antagonism of subconjunctival PPP with regard to protein leakage found in the present study and the strong inhibitory effect on the intraocular pressure increase reported by others (Whitelocke & Eakins 1973 Bethel & Eakins 1971a b)

Further it has been shown by Bethel & Eakins (1971a) that the strongest PG antagonistic action of PPP resides in the low molecular weight fraction of PPP since this fraction is 2 to 5 times more potent than PPP itself as an inhibitor of the intraocular pressure increase to PGs In the present study 5 mg subconjunctival DPP was however not superior to 10 mg PPP as an inhibitor of the aqueous flare response to PGE_1 and further DPP caused local irritation and protein leakage in about the same percent of eyes as did PPP DPP is at present not available in amounts great enough for testing its antiprostaglandin effects when administered generally

Cole (1961) has shown that a dose of 100 mg intravenous PPP is sufficient for total blocking of the intraocular pressure increase and for reduction of the flare response to topical HCl mustine in rabbits For the traumatic stimuli tested in the present study significant action of 100 mg PPP on the flare increase could not be recorded but a dose of 200 mg intravenous PPP (about 75–100 mg/kg bodyweight) was required for significant inhibition of the protein leakage to PGE_1 or α MSH whereas even this dose was insufficient for effective blocking of the PGE action However if the same dose (75–100 mg/kg bodyweight) of PPP was administered subcutaneously the aqueous flare response was markedly decreased for all three irritative stimuli tested This indicates that the prolonged availability of a moderate concentration of PPP caused by subcutaneous administration is more favourable for prostaglandin antagonism than is the comparatively higher concentration reached after intravenous injection a concentration which comparatively rapidly may decline to ineffective levels

Eakins et al (1970) have reported that 200 mg/kg bodyweight PPP given intravenously produced severe alterations in blood pressure However 100 mg/kg bodyweight PPP showed no or only minor pressure effects so the PPP actions on the flare response in the present study is probably not considerably disturbed by blood pressure changes

The purpose of this study was to find out whether the damaging effects of α MSH on the blood aqueous barrier are in some way dependent on PG activity

though the α MSH effects have been shown earlier to differ from PG actions in many respects (Bengtsson 1975 1976 Bengtsson & Ehinger 1977)

The present results provide support for two possible suggestions Assuming that PPP is a specific PG antagonist (Eakins et al 1970) the present results support earlier studies indicating that PGs take part in the barrier damaging action of α MSH not via enhanced PG synthesis (Bengtsson 1975) but possibly by pathologically increased PG accumulation in the iris and ciliary body (Bengtsson & Ehinger 1977) On the other hand it has not been proved at which cellular level PPP exerts its PG antagonism in the eye It may be possible that the action of PPP is not due to inhibition at the PG receptor level but at a later stage in the course of reactions Studies on other biological systems support this hypothesis For bovine thyroid cells it has been shown that PPP exerts its PG antagonism by inhibiting the stimulatory effects of PGE on adenyl cyclase (Burke & Sato 1971) and in mouse ovaries and rabbit myometrium PPP inhibits PG effects at a step subsequent to PG *induced stimulation* of adenyl cyclase (Kuehl Jr et al 1971) cAMP might be the ultimate barrier disturbing factor mediating PG as well as α MSH effects in the eye This hypothesis does not however preclude the possibility that PGs take part in the barrier damaging effect of α MSH

References

Beitch B R & Eakins K E (1969) The effects of prostaglandins on the intraocular pressure of the rabbit *Brit J Pharmacol 37* 158–167

Bengtsson E (1975) The inhibiting effect of indomethacin on the disruption of the blood aqueous barrier in the rabbit eye With a technical note Krakau C E T & Öhman R Measurement of the aqueous flare *Invest Ophthalmol 14* 306–312

Bengtsson E (1976) The effect of imidazole on the disruption of the blood aqueous barrier in the rabbit eye *Invest Ophthalmol 15* 315–320

Bengtsson E & Ehinger B (1977) The effect of experimental uveitis on the uptake of prostaglandin E_1 in the rabbit iris ciliary body *Acta ophthal (Kbh) 55* 683–695

Bethel R A & Eakins K E (1971a) The mechanism of the antagonism of experimentally induced ocular hypertension by polyphloretin phosphate *Exp Eye Res 13* 83–91

Bethel R A & Eakins K (1971b) Antagonism by polyphloretin phosphate of the intra ocular pressure rise induced by prostaglandin and formaldehyde in the rabbit eye *Fed Proc 30* 626

Burke G & Sato S (1971) Effects of long acting thyroid stimulator and prostaglandin antagonists on adenyl cyclase activity in isolated bovine thyroid cells *Life Sci 10* 969–981

Butcher R W & Sutherland E W (1962) Adenosine 3 5 phosphate in biological materials *J biol Chem 237* 1244–1250

Cole D F (1961) Prevention of experimental ocular hypertension with polyphloretin phosphate *Brit J Ophthal 45* 482–489

Eakins K E Karim S M M & Miller J D (1970) Antagonism of some smooth muscle actions of prostaglandins by polyphloretin phosphate *Brit J Pharmacol 39* 556–563
Kelly R G M & Starr M S (1971) Effects of prostaglandins and a prostaglandin antagonist on intraocular pressure and protein in the monkey eye *Canad J Ophthal 6* 205–211
Kuehl Jr F A, Humes K L, Mandel I E Cirillo V J Zanetti M E & Ham F A (1971) Prostaglandin antagonists studies on the mode of action of polyphloretin phosphate *Biochem Biophys Res Commun 41* 1464–1470
Neufeld A H Jampol L M & Sears M L (1972) Aspirin prevents the disruption of the blood aqueous barrier in the rabbit eye *Nature (Lond) 238* 158–159
Vane J R (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirinlike drugs *Nature New Biol 231* 232–235
Waitzman M B & Woods W D (1971) Some characteristics of an adenyl cyclase preparation from rabbit ciliary process tissue *Exp Eye Res 12* 99–111
Whitelocke A F & Eakins K E (1973) Vascular changes in the anterior uvea of the rabbit produced by prostaglandins *Arch Ophthal (Chicago) 89* 495–499
Zink H A Podos S M & Becker B (1973) Inhibition by imidazole of the increase in intraocular pressure induced by topical prostaglandin E *Nature New Biol 245* 21–23

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NORMAL VALUES IN CLINICAL ELECTROOCULOGRAPHY

V Variability Within and Between Eyes

BY

ERIK KROGH

Three EOG s (DC amplified 30 degree saccades slightly modified Arden schedule) were recorded at weekly intervals from each of 16 normal human eyes (eight subjects) The light induced potential rise of the dark adapted eye the Arden ratio and the Gliem ratio entered into the analysis of intra and inter eye variation The 95 % confidence intervals for the mean parameter values of each eye were ± 59 μV (mean = 415 μV) for the light induced potential rise ± 22 (mean = 260) for the Arden ratio and ± 10 (mean = 92) for the Gliem ratio The intra eye variability was compared to earlier studies of the day to day variation of the ERG by means of a dimensionless index no substantial differences were found Highly significant differences in the EOG parameter levels existed between the subjects whereas the variation between right eye and left eye means in the individual subjects was insignificant The Gliem ratio offered no advantage over the Arden ratio in these respects The primarily qualitative nature of the EOG in the present version is emphasized by the present results

Key words electrophysiology – electrooculography – EOG – variability – normal values

The variation and co variation of 142 single electrooculograms (EOG s) recorded in normal human eyes have been analysed in previous papers (Krogh 1975 1976 1977a b) In spite of various attempts to improve the well established Arden

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recording procedure (Arden et al 1962) the test parameters were characterized by a considerable scale width which was explained to only a small extent by co variation between the EOG and other variables of the subjects A sometimes remarkable individual right left difference between the EOG parameters in otherwise similar eyes suggested a low intra individual test precision which has in fact been claimed to characterize the original Arden procedure (Kelsey 1967 Muller & Haase 1970)

The present paper deals with the inter and intra eye variability as illustrated by repeated EOG recordings in a smaller sample of normal human subjects The following EOG parameters will enter into the analysis 1) The difference (L D) between the maximal potential value during light stimulation (light peak L) and the minimal potential during dark adaptation (dark trough D) 2) the Arden ratio ($\frac{L}{D} \times 100$) and 3) the Gliem ratio ($\frac{L-D}{B} \times 100$) where B refers to a base potential value (see below) The author has presented the theoretical considerations behind these three parameters in the above mentioned papers together with the analysis of their inter subject variability and it was found of interest to examine their intra eye variation with respect to their value in the clinical evaluation of the EOG Finally the EOG intra eye variability is compared with similar studies of the normal human scotopic b wave of the electro retinogram (ERG)

Material

Eight healthy medical students (seven males one female age 25–27 years) served as test subjects They had no visual complaints and a clinical examination according to a previously described programme (Krogh 1975) disclosed no extreme or pathological values of the refractive state axial length of the eye as measured by means of ultra sonography corneal diameter and curvature pupillary diameter degree of ocular protrusion and iris pigmentation and interpupillary distance Likewise slit lamp examination and ophthalmoscopy were normal in every case

Methods

EOG RECORDING PROCEDURE

Lead alloy skin electrodes were attached outside the canthi of both eyes and connected to a Mingograph (Siemens type M34) The subjects performed each minute approximately ten 30 degree saccades with the aid of a metronome and small red fixation lights The saccades were DC amplified (bandwidth 0–15 Hz gain 20–40 μV/mm) and the resulting ink trace was measured with a slide gauge The average value for each train of saccades was then transformed into an EOG potential value

The stimulus sequence was initiated by 10 min of strong light adaptation (4000 lx in the central part of the gaze field decreasing to 2500 lx in the periphery) at the end of which the first potential value was recorded (the base potential according to Gliem s procedure (1971)) Thereafter the subject was dark adapted until the dark troughs could be recognized The stimulus light was then switched on again until the light peaks were apparent

Each subject was examined three times at weekly intervals The examinations took place at the same time of the day and effort was made to secure equal test conditions in the three recording situations

STATISTICAL ANALYSIS

Repeated measurements are generally distributed normally The presently analysed EOG parameters however pose a particular problem because potential values and quotients of them cannot both follow a gaussian distribution Nevertheless the samplin distribution of *mean* values will approximate to a normal distribution according to *the central limit theorem* (see Campbell 1974) Also the variance of the mean will be related to the variance of the original – not necessarily normal – distribution by the formula

$$\textit{sample mean variance } (s^2_m) = \frac{\textit{variance of original distribution } (s^2)}{\textit{sample size}} \qquad (1)$$

An estimate of the variance in k groups not necessarily having identical means is obtained from the following expression

$$s^2_{(\textit{with groups})} = \frac{\sum_{r=1}^{k} f_r \times s^2_r}{\sum_{r=1}^{k} f_r} \qquad (2)$$

where f_r *and* s^2_r are the degrees of freedom and the variance of sample r The validity of formula (2) requires that the variance in the k groups does not differ substantially This prerequisite is tested in the present analysis with Bartlett s test for homogeneity of variance

95 % confidence intervals for the mean value of each eye are calculated by means of s and a Student t value of 2 131 ($P = 0\,05$ 15 degrees of freedom)

The *between groups* variance is related to the *within groups* variance by means of Fisher s F statistic

Karpe (1945) and later Spivey & Pearlman (1963) estimated the day to day variability of the scotopic b wave of the human and rabbit ERG by means of the quantity

$$\frac{\textit{parameter range}}{\textit{smallest parameter value}} \times 100 \qquad (3)$$

The dependence on the extreme test values gives this expression a somewhat accidental character and moreover its scale location is affected by the number of observations in each group The present author therefore chose to present median values only – and not the ranges – of this quantity as concerns the EOG parameters

Results

Fig 1 shows the distribution of the three measurements of the parameter *L D* from each eye The intra eye variability is apparent and the degree of parallelism between the recordings from the two eyes of each subject is moderate Fig 2 shows the distribution of the Arden ratio and it is seen that the degree of individual right eye left eye parallelism is slightly larger Fig 3 shows the similarly arranged figures of the Gliem ratio In two recordings a base value could not be obtained because of large electrode off set potentials and consequently only 46 Gliem ratios enter into the analysis

Bartlett s test gave no reason to suspect significant differences in variance between the 16 samples ($P > 0\ 1$ for all three parameters) The variances in

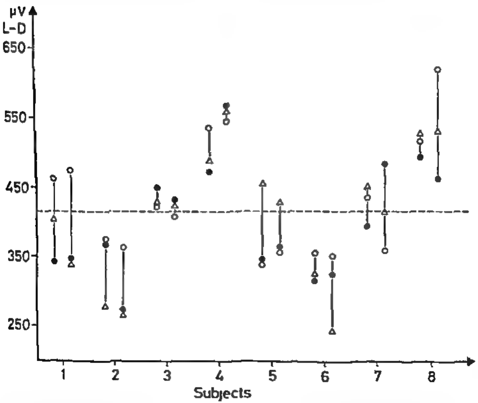

Fig 1

Graphical presentation of the 48 recordings of the light induced potential rise of the dark adapted eye Right eye values precede left eye values in each subject The first second and third examination are represented by open circles filled circles and triangles respectively The dotted line marks the sample mean

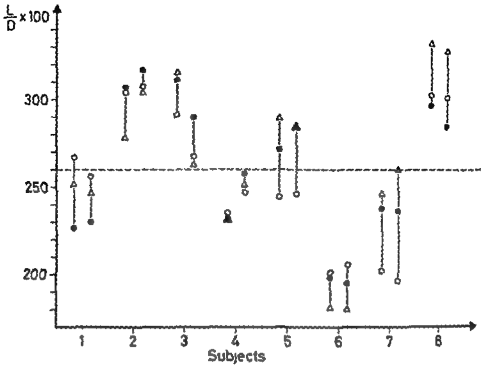

Fig 2

Graphical presentation of the 48 recordings of the Arden ratio Symbols as in Fig 1

Table I were therefore calculated as a starting point A highly significant inter eye variation characterizes this sample and Figs 1 2 and 3 suggest that most of this variation arises in an inter subject variability This is confirmed by an analysis of variance based upon the subjects and initiated by comparing the variance between eyes/within each subject to the variance within eyes The differences between each subject s right and left eye means were not significant (variance ratio less than one for all three parameters) and consequently these two variance estimates were joined into a *within subjects* variance against which the between subject variance is tested (Table I)

Table II gives the *within eyes* variability as the square root *s* An estimate of the *relative* dispersion (Pearson s coefficient) is obtained by relating this quantity to the sample mean The Arden ratio presents the smallest value but the lack of a significance test of such differences must be emphasized

The 95 % confidence intervals for the mean values of three FOC recordings (and in case of the Gliem ratio also for the mean of two recordings) are also to be found in Table II It must be concluded that even a mean parameter value based upon three (two) recordings is subject to considerable variability

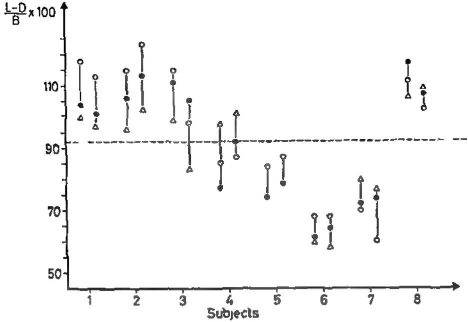

Fig 3

Graphical presentation of the 46 recordings of the Gliem ratio
Symbols as in Fig 1

Table 1

Analysis of variance of repeated EOG recordings in normal human subjects s = the variance as specified in the initial column

s	Light induced potential rise of the dark adapted eye	Arden ratio	Gliem ratio
Between eyes	18561	4439	893
Within eyes	2347	315	64
Variance ratio	7 9 ($P < 0\,001$)	14 1 ($P < 0\,001$)	14 0 ($P < 0\,001$)
Between subjects	38313	9278	1855
Within subjects	2136	313	63
Variance ratio	17 9 ($P < 0\,001$)	29 6 ($P < 0\,001$)	29 4 ($P < 0\,001$)

Table II

The within eyes variability of three EOG parameters The figure in brackets refers to the groups containing only two Gliem ratios s = the standard deviation (square root of the variance)

	Light induced potential rise of the dark adapted eye	Arden ratio	Gliem ratio
s *(within eyes)*	48 μV	18	8
$\bar{x}$ *(total sample)*	415 μV	260	92
$\frac{s}{\bar{x}} \times 100$ (coefficient of variation)	12	7	9
95 % confidence intervals for the mean of 3 (2) recordings from the same eye	± 59 μV	± 22	± 10 (1*)
Median of *range × 100/smallest value*	27	12	17

Discussion

The present *analysis demonstrates that repeated EOG recordings from the same eye using the technique described are characterized by somewhat low precision Moreover changing EOG values in one eye are not always* accompanied by changes in the fellow eye in the same direction and of comparable *magnitude* The 95 % confidence intervals of the mean values *in the present* analysis are quite large but would diminish if more than three recordings were performed However this is hardly the way to increase the *precision* of the clinical EOG

In Karpe s study (1945) of the variability of the human scotopic *b* wave the expression *range × 100/smallest value* never surpassed 15 but most of his subjects were examined only twice The median value is 7 (present author s calculation) The figures from the human recordings in the study of Spivey & Pearlman (1963) ranged from 16 to nearly 100 with a median of approximately

40 (this author s estimate) but these values were derived from six recordings (three figures from each of the two eyes of a subject) The variability of the rabbit *b* wave was also tested (four recordings from the same eye) and in this case the range and the median of the quantity referred to above were approximately 25–70 and 50 (this author s estimate) These figures admittedly make a rough estimate but nevertheless a comparison with Table II (last row) in the present paper suggests that the day to day variability of the EOG does not differ substantially from that of the ERG

The highly significant inter subject differences in the EOG parameter levels cannot be explained by this or earlier investigations In keeping with the author s earlier studies of 142 single EOG s the Gliem ratio offered no advantage over the Arden ratio in the presently analysed respects and the primarily qualitative nature of the EOG recording in the present version is further underlined

References

Arden G B Barrada A & Kelsey J H (1962) New clinical test of retinal function based upon the standing potential of the eye *Brit J Ophthal 46* 449–467

Campbell R C (1974) *Statistics for biologists* 2nd ed Cambridge University Press

Gliem H (1971) *Das Elektrookulogramm Ein Erfahrungsbericht* Abhandlungen aus dem Gebiete der Augenheilkunde Band 40 VEB Georg Thieme Leipzig

Karpe G (1945) *The basis of clinical electroretinography Acta ophthal (Kbh)* Supplementum XXIV

Kelsey J H (1967) Variations in the normal electro oculogram *Brit J Ophthal 51* 44–49

Krogh E (1975) Normal values in clinical electrooculography I Material method methodological investigations and distribution of the potential and time parameters *Acta ophthal (Kbh) 53* 563–575

Krogh E (1976) Normal values in clinical electrooculography II Analysis of potential and time parameters and their relation to other variables *Acta ophthal (Kbh) 54* 389–400

Krogh E (1977a) Normal values in clinical electrooculography III Numerical evaluation of two dimensionless EOG parameters *Acta ophthal (Kbh) 55* 227–236

Krogh E (1977b) Normal values in clinical electrooculography IV Analysis of two dimensionless EOG parameters and their relation to other variables *Acta ophthal (Kbh) 55* 739–749

Muller W & Haase E (1970) Inter und intraindividuelle Streuung im EOG *Albrecht v Graefes Arch klin exp Ophthal 181* 71–78

Spivey B E & Pearlman J T (1963) Day to day variations in the ERG of humans and rabbits *Amer J Ophthal 55* 1013-1020

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CHANGES IN ULTRASTRUCTURE AND FUNCTION OF THE SHEEP PIGMENT EPITHELIUM AND RETINA INDUCED BY SODIUM IODATE[1]

I. The Ultrastructure of the Normal Pigment Epithelium of the Sheep

BY

SVEN ERIK G. NILSSON, BENGT KNAVE and HANS E. PERSSON

The normal ultrastructure of the sheep pigment epithelial cells is described as a basis for the interpretation of toxic (sodium iodate) effects on these cells dealt with in two following papers. The morphological features of the different cell membranes and cell organelles, particularly the phagosomes and the lipid droplets, are discussed in relation to renewal of the photoreceptor outer segment, pigment epithelial and retinal metabolism, barrier mechanisms and electrical properties.

Key words: electron microscopy – pigment epithelium – retina – sheep.

The ERG waves arise as the result of an integration of several underlying processes in the neuroretina and the pigment epithelium. In one of our earlier investigations (Knave, Persson & Nilsson 1974) sodium iodate was used with

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the intention to selectively block the activity of the pigment epithelium while studying the influence of barbiturate on the neuroretina of the sheep Such a model can probably be used also in experiments concerning other drugs For this purpose it would be desirable to know in more detail the nature of and the correlation of the changes in pigment epithelial and retinal ultrastructure and function induced by sodium iodate In this connection particularly the early changes are of interest Previous studies on the subject (Noell 1953 1954 1963 Grignolo et al 1966 Suyama 1965 Babel 1970) either do not include histology of the early stages or do not correlate morphological findings with electro retinography however

For this reason an investigation was undertaken to map and to correlate mainly the early changes in ultrastructure and ERG of the sheep pigment epi thelium and retina after administration of sodium iodate For the necessary background as to the normal ultrastructure of the sheep neuroretina the reader is referred to earlier papers (Nilsson Knave Persson & Lunt 1973 Nilsson Knave Lunt & Persson 1973) but with respect to the pigment epithelium the studies already available (Leure duPree 1968 Nilsson Knave Persson & Lunt 1973) needed to be completed with additional material Thus this first paper in a series of three describes the normal ultrastructure of the sheep pigment epithelium The other two papers will deal with the early and the delayed effects of sodium iodate respectively (Nilsson Knave & Persson 1977a b)

Material and Methods

The eyes from two light adapted (for about 8 h) domestic sheep were fixed by perfusion via the common carotid arteries with 1 % glutaraldehyde in 0 1 M cacodylate buffer Thereafter the eyes were enucleated The anterior segment of each eye was removed and fixation was continued for three days by means of immersion in the same fixative Then the eyes were cut in smaller pieces and the sclera and most of the choroid were dissected away At this stage such a dissection could be performed without giving rise to retinal detachment 1 % osmium tetroxide in the same buffer was used for post fixation, and after dehydration in acetone the specimens were embedded in Vestopal W Pieces of retina and the pigment epithelium taken from the extratapetal area of the posterior part of the eye were sectioned for light and electron microscopy The thin sections were examined in a Philips 300 electron microscope

Observations

The nucleus of the pigment epithelial cell was generally oval and located in the basal part of the cell It was often seen to contain a nucleolus (Fig 1)

The apical plasma membrane showed slender processes coming into close contact with the rod outer segments (Fig 1) Attachment zones (junctional complexes) were present between the lateral membranes of adjacent cells not far from the apical surface of the cell (Fig 1) Melanin pigment granules of different sizes and shapes mainly elongated were abundant except close to the basal plasma membrane (Figs 1 and 5)

A moderate number of rod shaped mitochondria were found in the basal half of the cell (Figs 2 and 4) The Golgi complex consisting of a number of flattened saccules and vesicles (Fig 2) was in most cases seen in the vicinity of the nucleus Rough surfaced endoplasmic reticulum and free ribosomes were observed most frequently in the basal part of the cell (Figs 3 and 4) Throughout the cytoplasmic compartment the very abundant tubular shaped profiles of the smooth surfaced endoplasmic reticulum were found (Fig 5) The basal plasma membrane was characterized by frequent infoldings (Fig 4) The basement membrane between the pigment epithelial cells and the endothelial cells of the choroidal capillaries is seen in Figs 3 and 4

In the apical part of the cell different kinds of granules and inclusion bodies were present From a morphological point of view the evenly light grey and membrane bound granules appear to contain lipids (Figs 5–7) Thus they are called lipid droplets The larger bodies are so called phagosomes containing incorporated outer segment discs (Figs 5–7) The phagosome (Ph 1) in Fig 5 shows fairly well organized and to a great extent parallel membranes whereas in Fig 6 as well as in Fig 7 a big phagosome (Ph 2) is seen to contain membranes in a concentric or an irregular arrangement Other phagosomes (Ph 3) were found to have a content of small bodies of concentrically arranged membranes or of a homogeneous substance (Figs 5 and 6) Occasionally also lipid droplets were observed within a phagosome (Ph 4) (Fig 6) The possible origin and function of the lightly stained granules labelled X in Fig 7 will be dealt with in the discussion

Discussion

The pigment epithelium described in the present investigation was taken from the extratapetal area of the fundus It contained a large number of melanin pigment granules as a striking difference from the melanin lacking pigment epithelium overlaying the tapetum (Nilsson Knave Persson & Lunt 1973) Many of the basic features of the melanin containing pigment epithelium of the sheep were also described by Leure duPree (1968)

Fig 1
Survey picture of a pigment epithelial cell (PE) N nucleus No nucleous M melanin granule A apical plasma membrane with processes Az attachment zone R rod outer segment × 14 500

The participation in the turnover of the rod outer segments is an important feature of the pigment epithelial cells It was shown by Nilsson (1964) that the outer segment disks in the young tadpole developed as invaginations of the plasma membrane at the base of the outer segment Since basal membrane invaginations of the same kind were observed also in adult receptor outer segments Nilsson (1964) proposed that new disks were formed in the same way also at the adult stage In elegant autoradiographic studies by Young (1967)

Fig 2
Mitochondria (Mi) and a Golgi complex (G) are seen in the basal half of the cell ×59 000

and by Young & Droz (1968) this idea was proven to be correct By the use of labelled amino acids it was found that the rod outer segment was continuously renewed from the base with a turnover time of 9–10 days for mouse and rat and about 6 weeks for frog It appears quite obvious that the same principle is valid also for the sheep

Young & Bok (1969) could demonstrate that the tips of the frog rod outer segments were repeatedly incorporated into the pigment epithelium where

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Figs 3 and 4
A basement membrane (BM) separates the pigment epithelial cell from the endothelial cell (E) of the choroidal capillaries The basal plasma membrane (B) shows numerous infoldings In the cytoplasm rough surfaced endoplasmic reticulum (RFR) free ribosomes (FR) and mitochondria (Mi) are seen ×27 500 and 34 000 resp


E
BM
RER
3

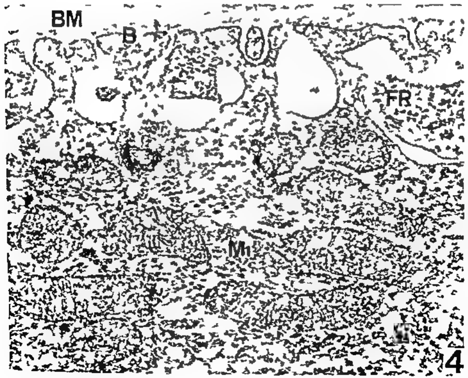
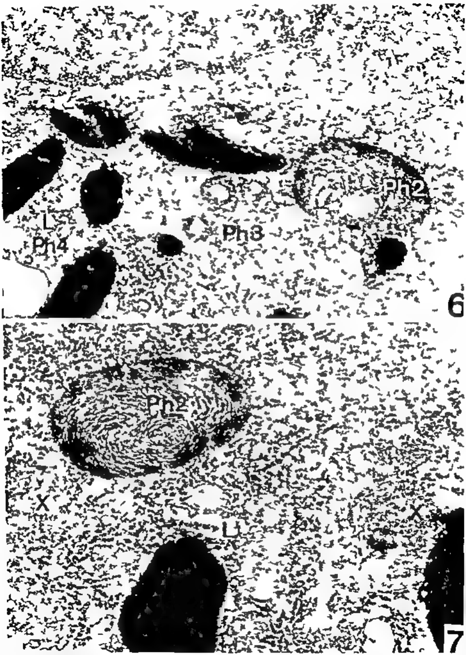

BM
B
FR
Mi
4

Fig 5

A phagosome with fairly well organized membranes (Ph 1) and a phagosome consisting of concentrically arranged membranes together with a homogeneous substance (Ph 3) are shown L lipid droplet SER profiles of smooth surfaced endoplasmic reticulum R rod outer segment ×42 000



Fi_s 6 and ,

Phagosomes containing concentrically and irregularly arranged membranes (Ph ?) small bodies of concentrically organized membraneous material (Ph 3) or lipid droplets (Ph 4) L lipid droplet \ lightly stained granules x 97 ,00 and 34 200 resp

so called phagosomes are formed Such inclusion bodies had been observed earlier (Dowling & Gibbons 1962, Bairati & Orzalesi 1963) but the exact nature of the structures was somewhat unclear It appears that the rod outer segment tip (about 5–40 disks) can be separated from the major part of the outer segment either by protrusion of pigment epithelial processes which latter then completely engulf the disks and withdraw them into the cell body of the pigment epithelial cell (Spitznas & Hogan 1970 (human)) or by shedding of the stack of disks primarily by infolding of the outer segment plasma membrane (Young 1971 (rhesus monkey)) Later it has been shown that also cone outer segments may be ensheathed by pigment epithelial processes (Steinberg & Wood 1974 (cat) Steinberg Wood & Hogan 1977 (human)) and that also the tip of cone outer segments can be engulfed into the pigment epithelium by protrusion of pigment epithelial processes (Hogan Wood & Steinberg 1974 Steinberg Wood & Hogan 1977 (human)) It has recently been shown that shedding of outer segment disks is a cyclic daily process where rods predominantly shed their disks at the onset of the light period (LaVail 1976 (rat) Basinger Hoffman & Matthes 1976 (frog)) and where shedding from cones occurs mainly at the beginning of the dark period (Young & O Day 1977 (goldfish)) In the present investigation the animals were dark adapted for about 8 h prior to the experiment

The phagosomes then undergo degradation through a series of stages (Ishikawa & Yamada 1970 Spitznas & Hogan 1970 Johnson 1975) The phagosomes labelled Ph 1–Ph 4 in Figs 5–7 of the present investigation are considered to represent successive stages in such a degradation The disintegration of the content seems to be accomplished by means of lytic enzymes such as acid phosphatase (Ishikawa & Yamada 1970 Marshall 1970 Hollyfield & Ward 1974) There are also morphological evidence supporting the idea that these enzymes may originate in the Golgi complex and that the enzymes then are stored in lysosomal granules which interact with the young phagosome (Ishikawa & Yamada 1970) The lightly stained granules (\) seen in Fig 7 could possibly represent such lysosomes However it cannot be excluded that they are instead final stages of phagosomal degradation The presence of cathepsin D (a proteolytic enzyme) in the pigment epithelium indicates that also this enzyme may take part in the digestion of the phagosomes (Hayasaka Hara & Mizuno 1975) Certain hereditary retinal degenerations can be explained by a defect in the phagocytic mechanism described above (Bok & Hall 1969 1971 Herron Riegel Myers & Rubin 1969 Herron Riegel Brennan & Rubin 1974)

The oil droplets of the frog pigment epithelium are known to concentrate vitamin A (the precursor of retinal) and fatty acids (Young & Bok 1970 Bibb &

Young 1974) It seems most likely that the lipid droplets of the sheep pigment epithelium correspond to the frog oil droplets It cannot be excluded that part of the lipid material is derived from outer segment degradation products

Besides the renewal of rod outer segments by means of membrane replacement both rods and cones renew their membranes also by diffuse molecular replacement This is true for proteins as well as for lipids It appears that the pigment epithelium plays an important role in lipid metabolism of outer segment membranes (Bibb & Young 1974 Young 1974)

The pigment epithelium is part of the blood retina barrier Its plasma membranes possess certain passive and active (selective) transport mechanisms (Steinberg & Miller 1973 Miller & Steinberg 1977a b) The extensive infoldings of the basal plasma membrane somewhat resemble those of the kindney tubular cells where extensive transport is known to take place Attachment zones (junctional complexes) connected the lateral membranes of adjacent cells Close to the apical surface of the cells they are of the tight junction type (zonulae occludentes) and just basally to the tight junctions zonulae adherentes are present (Leure duPree 1968) It was clearly shown by Peyman Spitznas & Straatsma (1971) that diffusion of peroxidase was abruptly stopped at the zonulae occludentes in the intercellular spaces of the pigment epithelium Thus the tight junctions together with the selective membrane transport mechanisms can effectively block free flux between the choroidal capillaries and the neuro retina The difference in transport and permeability properties between the apical and the basal membranes of the pigment epithelial cells gives rise to the trans pigment epithelial potential (Steinberg & Miller 1973 Miller & Steinberg 1977a b) which appears to be the major component of the standing potential of the eye (Noell 1954 Heck & Papst 1957 Gouras 1969) Toxic agents that affect the properties of the basal and/or apical membranes are thus very likely to influence the trans pigment epithelial potential and hence the standing potential of the eye Furthermore it is to be expected that the *c* wave of the ERG which is generated mainly across the apical membrane of the pigment epithelium (Steinberg Schmidt & Brown 1970 Schmidt & Steinberg 1971 Steinberg & Miller 1973 Oakley & Green 1976) is also affected at the same time Sodium iodate is a toxic agent of this kind which will be shown in the following papers (Nilsson Knave & Persson 1977a b)

In conclusion it can be said that the pigment epithelium is a most important barrier layer as well as a very metabolically active layer interposed between the receptor cells and the circulation and upon which the receptor cells are highly dependent

References

Babel J (1970) The retina In Bischoff A Ed *Ultrastructure of the Peripheral Nervous System and Sense Organs* pp 339–441 G Thieme Verlag Stuttgart

Bairati A Jr & Orzalesi N (1963) The ultrastructure of the pigment epithelium and of the photoreceptor pigment epithelium junction in the human retina *J Ultrastruct Res* [redacted] 484–496

Basinger S Hoffman R & Matthes [redacted] (1976) Photoreceptor shedding is initiated by light in the frog retina *Science 194* 1074–1076

Bok D & Hall M O (1969) The etiology of retinal dystrophy in RCS rats *Invest Ophthal* 8 649–650

Bok D & Hall M O (1971) The role of the pigment epithelium in the etiology of inherited retinal dystrophy in the rat *J Cell Biol 49* 664–682

Bibb C & Young R W (1974) Renewal of fatty acids in the membranes of visual cell outer segments *J Cell Biol 61* 327–343

Dowling J E & Gibbons I R (1962) The fine structure of the pigment epithelium in the albino rat *J Cell Biol 14* 459–474

Gouras P (1969) Clinical electro oculography In Straatsma B R Ed *The Retina* pp 565–581 University of California Press Berkeley & Los Angeles

Grignolo A Orzalesi N & Calabria G A (1966) Studies on the fine structure and the rhodopsin cycle of the rabbit retina in experimental degeneration induced by sodium iodate *Exp Eye Res 5* 86–97

Hayasaka S Hara S & Mizuno K (1975) Distribution and some properties of cathepsin [redacted] in the retinal pigment epithelium *Exp Eye Res 21* 307–313

Heck J & Papst W (1957) Über den Ursprung des corneo retinalen Ruhepotentials *Bibl ophthal (Basel) 48* 96–107

Herron W L Riegel [redacted] W Myers O [redacted] & Rubin M L (1969) Retinal dystrophy in the rat – A pigment epithelial disease *Invest Ophthal 8* 595–604

Herron W L Riegel B W Brennan E & Rubin M L (1974) Retinal dystrophy in the pigmented rat *Invest Ophthal 13* 87–94

Hogan M J Wood I & Steinberg R [redacted] (1974) Phagocytosis by pigment epithelium of human retinal cones *Nature (Lond) 252* 305–307

Hollyfield J G & Ward A (1974) Phagocytic activity of the pigmented retinal epithelium III Interaction between lysosomes and ingested polystyrene spheres *Invest Ophthal 13* 1016–1023

Ishikawa T & Yamada E (1970) The degradation of the photoreceptor outer segment within the pigment epithelial cell of the rat retina *J Electron Microscopy 19* 85–99

Johnson N F (1975) Phagocytosis in the normal and ischaemic retinal pigment epithelium of the rabbit *Exp Eye Res 20* 9–10

Knave [redacted] Persson H E & Nilsson S E G (1974) The effect of barbiturate on retinal functions II Effects on the c wave of the electroretinogram and the standing potential of the sheep eye *Acta physiol scand 91* 180–186

LaVail M M (1976) Rod outer segment disk shedding in rat retina relationship to cyclic lighting *Science 194* 1071–1073

Leure duPree A (1968) Ultrastructure of the pigment epithelium in the domestic sheep *Amer J Ophthal 65* 383 393

Marshall J (1970) Acid phosphatase activity in the retinal pigment epithelium *Vision Res 10* 891–894

Miller S S & Steinberg R H (1977a) Passive ionic properties of frog retinal pigment epithelium In preparation for publication

Miller S S & Steinberg R H (1977b) Active transport of ions across frog retinal pigment epithelium In preparation for publication

Nilsson S E G (1964) Receptor cell outer segment development and ultrastructure of the disk membranes in the retina of the tadpole (*Rana pipiens*) *J Ultrastruct Res 11* 581–620

Nilsson S E G Knave B Lunt T & Persson H E (1973) The morphology of the sheep retina II The inner nuclear layer the ganglion cells and the plexiform layers *Acta ophthal (Kbh) 51* 612–627

Nilsson S E G Knave B & Persson H E (1977a) Changes in ultrastructure and function of the sheep pigment epithelium and retina induced by sodium iodate II Early effects *Acta ophthal (Kbh) 55* 1007–1026

Nilsson S E G Knave B & Persson H E (1977b) Changes in ultrastructure and function of the sheep pigment epithelium and retina induced by sodium iodate III Delayed effects *Acta ophthal (Kbh) 55* 1027–1043

Nilsson S E G Knave B Persson H E & Lunt T (1973) The morphology of the sheep retina I The receptor cells and the pigment epithelium *Acta ophthal (Kbh) 51* 599–611

Noell W K (1953) Studies on the electrophysiology and the metabolism of the retina *Project report U S Air Force SAM Project No 21-1201-0004* pp 1–122 Randolph Field Texas

Noell W K (1954) The origin of the electroretinogram. *Amer J Ophthal 38* 78–93

Noell W K (1963) Cellular physiology of the retina *J opt Soc Amer 53* 36–48

Oakley II B & Green D G (1976) Correlation of light induced changes in retinal extracellular potassium concentration with c wave of the electroretinogram. *J Neurophysiol 39* 1117–1133

Peyman G A Spitznas M & Straatsma B R (1971) Peroxidase diffusion in the normal and photocoagulated retina *Invest Ophthal 10* 181–189

Schmidt R & Steinberg R H (1971) Rod dependent intracellular responses to light recorded from the pigment epithelium of the cat retina *J Physiol (Lond) 217* 71–91

Spitznas M & Hogan M J (1970) Outer segments of photoreceptors and the retinal pigment epithelium *Arch Ophthal (Chicago) 84* 810–819

Steinberg R H & Miller S (1973) Aspects of electrolyte transport in frog pigment epithelium *Exp Eye Res 16* 365–372

Steinberg R H Schmidt R & Brown K T (1970) Intracellular responses to light from cat pigment epithelium origin of the electroretinogram c wave *Nature (Lond) 227* 728–730

Steinberg R H & Wood I (1974) Pigment epithelial cell ensheathment of cone outer segments in the retina of the domestic cat *Proc roy Soc Lond B 187* 461–478

Steinberg R H Wood I & Hogan M J (1977) Pigment epithelial ensheathment and phagocytosis of extrafoveal cones in human retina *Philosoph Trans R Soc Lond B 277* 459–474

Suyama T (1965) Electron microscopic study on experimental retinal degeneration induced by sodium iodate injection. *Acta Soc ophthal jap 69* 440–460

Young R W (1967) The renewal of photoreceptor cell outer segments *J Cell Biol* *33* 61–72
Young R W (1971) Shedding of discs from rod outer segments in the rhesus monkey *J Ultrastruct Res* *34* 190–203
Young R W (1974) Biogenesis and renewal of visual cell outer segment membranes *Exp Eye Res* *18* 215–223
Young R W & Bok D (1969) Participation of the retinal pigment epithelium in the rod outer segment renewal process *J Cell Biol* *42* 392–403
Young R W & Bok D (1970) Autoradiographic studies on the metabolism of the retinal pigment epithelium *Invest Ophthal* *9* 524–536
Young R W & Droz B (1968) The renewal of protein in retinal rods and cones *J Cell Biol* *39* 169–184
Young R W & O Day W T (1977) Personal communication

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CHANGES IN ULTRASTRUCTURE AND FUNCTION OF THE SHEEP PIGMENT EPITHELIUM AND RETINA INDUCED BY SODIUM IODATE[1]

II Early Effects

BY

SVEN ERIK G NILSSON BENGT KNAVE and HANS E PERSSON

The present investigation shows that the membrane properties of the sheep pigment epithelial cells were very rapidly and severely affected by sodium iodate whereas the effects concerning the neuroretina were delayed The c wave of the ERG was immediately abolished and replaced by a cornea negative potential but the *a* and *b* waves were preserved for about 80–100 min Ultrastructurally the plasma membranes (particularly the basal plasma membrane) of the pigment epithelial cells were destroyed or less distinct than normally The cell organelles were swollen and rup tured There were indications that the pigment epithelium could no longer participate in the receptor outer segment turnover The photoreceptor cells were morphologically undamaged and few or no signs of injury were ob served in the inner layers of the retina The effects upon the neuroretinal functions seen after 80–100 min consisting of a reduction of *a* and *b* wave amplitudes were most likely caused by an inability of the pigment epi

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thelium to maintain in the long run its metabolic and barrier properties It appears that at an early stage after sodium iodate injection the present preparation may be useful for the study of the effects on the neuro retina proper of drugs and other agents

Key words electron microscopy – electroretinography – *c* wave – pigment epithelium – retina – sodium iodate – toxicity – sheep

Changes in the *a* and *b* waves of the ERG are generally considered to represent events in the neuroretina whereas a change in the *c* wave would reflect a pigment epithelial involvement The *a* wave (Brown & Watanabe 1962 Murakami & Kaneko 1966 Tomita Murakami & Pautler 1967) and the *b* wave (Brown & Wiesel 1961a b Steinberg 1969 Miller & Dowling 1970) are well known to be generated in the retina proper Noell (1953 1954 1963) and Brown & Wiesel (1961b) found strong evidence that the *c* wave originated to a great extent in the pigment epithelium Since then it has been shown that the *c* wave represents the hyperpolarization mainly of the apical membrane of the pigment epithelial cells in response to the rod initiated decrease in external potassium in the space surrounding the photoreceptors that occurs during light stimulation (Steinberg Schmidt & Brown 1970 Schmidt & Steinberg 1971 Steinberg & Miller 1973 Oakley & Green 1976) In addition it is very likely that the *c* wave is affected by other neuroretinal activities e g slow P III a slow negative potential (Granit 1947) with at least two subcomponents from the distal part of the receptors and from the inner nuclear layer respectively (Murakami & Kaneko 1966 Hanitzsch 1973)

In many cases there is a need of separating the pigment epithelial responses from the potentials of the neuroretina Thus sodium iodate has been used with the intention to selectively block the activity of the pigment epithelium while searching for possible effects of other agents or drugs on the neuroretina (Noell 1953 1954 (azide iodoacetic acid) Knave Persson & Nilsson 1974 (barbiturate)) *The same model might be useful also in connection* with the study of different drugs or perhaps as a more general way of distinguishing between retinal and pigment epithelial responses In order to further facilitate the interpretation of results obtained under such circumstances it appears necessary to have access to a description of and a correlation of particularly the early changes in ultrastructure and function of the pigment epithelium and retina induced by sodium iodate However earlier studies on the subject either do not include histology of the early stages or do not correlate ultrastructural findings with electrophysiology

The effects of sodium iodate (3 ml of a 5 per cent solution intravenously) on the rabbit retina and pigment epithelium were studied extensively by Noell (1953 1954

1958 1959 1963) Based upon ERG recording and light microscopy Noell found that the pigment epithelium was affected by iodate earlier than the receptor cells The c wave of the ERG disappeared within a few minutes and was replaced by a cornea negative potential (the azide insensitive potential) Not until after two to six h where the *a* and *b* waves affected (after moderate doses of iodate) The *a* wave was increased and the *b* wave decreased in amplitude At 24 h the *a* and *b* waves were both increased in amplitude but the latency of the response was prolonged On the fifth day the *a* wave had almost completely disappeared and between the eighth and fourteen h day the *b* wave was minimal or had disappeared The histology was not examined until the fourth day after the injection however and at that stage the pigmen epithelium was almost completely destroyed Furthermore also the rod outer segment had degenerated to a great extent Thus the earliest structural changes were not followed

Grignolo Orzalesi & Calabria (1966) investigated changes in the ultrastructure and the rhodopsin cycle of the rabbit eye af er administration of sodium iodate (a single dose of 30 mg/kg b wt) The first structural changes appeared seven to ten h after the injection and concerned the pigment epithelium only They included e g swollen mitochondria and vesiculated endoplasmic reticulum Certain cells showed more advanced alterations and after more than ten h all pigment epithelial cells were severely damaged with disorganized cell boundaries membrane whirls and shrunken nuclei At 15–20 h the distal ends of the Muller cells appeared swollen Not until 25–28 h after the injection did changes appear in the receptor cells The outer segments showed disrupted limiting membranes and disorganized disks After four to five days the outer segments disappeared The inner segments remained unchanged or almost unchanged throughout the investigation Four to six days after the administration of sodium iodate some repairing process began mainly in the pigment epithelium where greatly modified pigmented cells with irregular shape inclusion bodies and cytoplasmic filaments appeared. However no migration of pigmented cells into the retinal layers was found The study clearly showed that the morphological changes of the pigment epithelium preceded those of the receptor cells The correlation in time to different ERG changes was not studied however

Suyama (1965) found that the disappearance of the *c* wave preceded that of the *a* and *b* waves which occurred 24 h after the third injection of sodium iodate in the rabbit i e 72 h after the first injection (Daily injections of 30 mg/kg b wt were given) Not until 48 h after the first injection were the first morphological changes observed At this stage structural alterations were seen not only in the pigment epithelium but also in the visual cells The pigment epithelial cells were destroyed more rapidly than the visual cells however Suyama apparently were not able to demonstrate the early pigment epithelial changes seen by Grignolo et al (1966)

Babel (1970) giving larger doses (60 mg/kg b wt) of sodium iodate to the rabbit did not study the ultrastructural changes until 24 h after the injection and the sequence of appearance of the different alterations is not quite clear The ERG could be extinguished as early as after 6 h

It is obvious that the literature shows many discrepancies with respect to the sequence and timing of the different changes seen after the administration of sodium iodate and in no case is a correlation between the early ultrastruc

tural changes and the ERG changes available As mentioned above for a more precise interpretation of results obtained from experiments where the effects of drugs or other agents on the retina are studied in combination with an intended blocking of the pigment epithelium by means of sodium iodate such early correlations seem to be highly desirable Furthermore species differences occur Lurie (1973) showed that the frog pigment epithelium and retina was fairly insensitive to sodium iodate Thus data from one species are not necessarily valid for another species

For reasons given above the present investigation was undertaken in order to describe in particular the early changes in ultrastructure of the pigment epithelium and the retina of the sheep after administration of sodium iodate and to correlate these changes to simultaneous alterations of the electroretinogram The normal ultrastructure of the neuroretina of the sheep was studied earlier (Nilsson Knave Persson & Lunt 1973 Nilsson Knave Lunt & Persson 1973) and that of the pigment epithelium was described in the first one (Nilsson Knave & Persson 1977a) of this series of three papers The third paper (Nilsson Knave & Persson 197?b) of this series will deal with the delayed effects of sodium iodate

Material and Methods

The results are based on two experiments performed on the intact and dark adapted sheep eye

The *a* *b* and *c* waves of the d c recorded ERG were followed in long term experiments according to a method earlier described in detail (Knave Møller & Persson 19?2) The tips of the recording and reference electrodes (matched calomel half cells) were placed on the cornea and subcutaneously at the upper bony margin of the orbit respectively and connected to the differential inputs of a low drift d c amplifier The signals were then fed into an analogue tape recorder as well as a signal analyzer and displayed

The duration of the stimulus light flashes was 1 0 sec and the intensity about 4.5 log rel units above the *b* wave threshold The intervals between the flashes were ? min The amplitude values were measured from the isoelectric line (*a* wave *c* wave and the negative so called azide insensitive potential replacing the *c* wave (Noell 195? 1954)) or from the trough of the *a* wave (*b* wave) In order to assure adequate measurements of the faster *a* and *b* waves they were measured from comparatively fast sweeps (Fig 2 b)

After stability was obtained in the ERG an iv injection of 30 mg sodium iodate ($NaIO_3$) per kg b wt was given (In the experiment illustrated in Fig 1 the injection was given at 90 min) About 80–100 min after the injection a decrease in *a* and *b* waves was seen Thereafter the ERG potentials were followed for another ?5–?0 min before fixation of the eyes was performed at about 100–150 min after the $NaIO_3$ injection The eyes were fixed by perfusion via the common carotid arteries with 1%

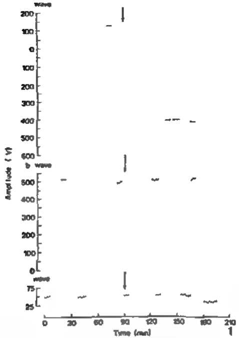

Fig 1

Effects of sodium iodate on the *a* *b* and *c* wave amplitudes of the ERG of the dark adapted sheep eye At 90 min (arrow) 30 mg $NaIO_3$ per kg b wt was given as an iv injection Stimulus duration 1 0 sec Stimulus intensity about 4 5 log rel units above *b* wave threshold

glutaraldehyde in 0 1 M cacodylate buffer and then prepared for electron microscopy according to the method described in the first paper of this series (Nilsson Knave & Persson 1977a)

Observations

Electrophysiology

The *a* *b* and *c* waves of the ERG (Figs 2 a and b) were recorded for at least 1.5 h before the injection of sodium iodate The *a* and *b* waves were quite stable but the *c* wave amplitude showed some initial oscillations with the well established frequency of two per h (Fig 1) In the experiment shown in Fig 1 the *c* wave amplitude stabilized at about 120–130 μV

Injection of sodium iodate immediately abolished the *c* wave which was replaced by a cornea negative potential During the first few minutes this change in the negative direction was dramatic amounting to about 300 μV

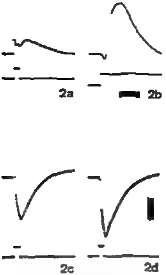

Fig 2

Representative ERG s from the experiment shown in Fig 1 a and b before treatment c 56 min after treatment with $NaIO_3$ d 100 min after treatment with $NaIO_3$ Records of type a c and d were used for measurements of the *c* wave and the negative potential replacing the *c* wave Records of type b were used for measurements of *a* and *b* waves For every registration both types of records were displayed from the tape recorder and photographed Stimulus duration 1 0 sec (indicated on lower line) Stimulus intensity about 4 5 log rel units above *b* wave threshold Amplitude calibration 200 μV Time calibration for record b 100 msec

(Fig 1) Thereafter the change proceeded at a slower rate and at 35–40 min after the injection the amplitude curve showed a plateau A typical record from this stage is demonstrated in Fig 2 c 40–65 min later (80–100 min after the injection) a further drop in potential levels was seen (Fig 1) At the termination of the experiment about 1 75–2 5 h after the injection the negative potential replacing the *c* wave had reached a value of approximately 550–750 μV below the isoelectric line

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Fig 3

Survey picture of sheep pigment epithelium (PE) and obliquely cut receptor outer and inner segments fixed for electron microscopy about 2 5 h after iv injection of sodium iodate Whereas the pigment epithelium has a speckled and swollen appearance the receptor cells look normal Concentrically arranged membrane whirls (MW) are seen at the border between the pigment epithelium and the rod outer segments RO rod outer segment CO cone outer segment RI rod inner segment CI cone inner segment 6100


PE
MW
RS
RI
CO
3

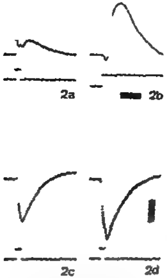

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Fig 3

Survey picture of sheep pigment epithelium (PE) and obliquely cut receptor outer and inner segments fixed for electron microscopy about 2.5 h after iv injection of sodium iodate Whereas the pigment epithelium has a speckled and swollen appearance the receptor cells look normal Concentrically arranged membrane whirls (MW) are seen at the border between the pigment epithelium and the rod outer segments RO rod outer segment CO cone outer segment RI rod inner segment CI cone inner segment × 6100

Sodium iodate did not significantly affect the *a* and *b* wave amplitudes initially However about 80–100 min later i e simultaneously with the second drop in amplitude of the negative potential replacing the *c* wave a marked decrease in *a* wave amplitude as well as a most prominent reduction of the *b* wave amplitude were found (Fig 1) A record from this period is shown in Fig 2 d

Thus a stage of 80–100 min duration when the *c* wave was abolished but when the *a* wave and *b* waves were unaffected could clearly be demonstrated

Ultrastructure

In survey pictures of the specimens fixed at termination of the experiments receptor cells seemed to be normal with respect to outer as well as inner segments (Fig 3) The pigment epithelium however had a swollen and mottled appearance Membrane whirls were seen at the border between the pigment epithelium and the rod outer segments

At higher magnification it became quite clear that the pigment epithelium with exception for the melanin granules had completely lost its normal structure The nucleus was pycnotic and the cytoplasm was swollen with aggregated cell organelles (Figs 4–6) The mitochondria as well as the tubules of the smooth surfaced endoplasmic reticulum were swollen and ruptured (Figs 4–6) In certain places the apical plasma membrane appeared to be less distinct than in normal tissue (Fig 5) As a typical feature of this stage whirls of membranes arranged concentrically (myelin figures) or in loops were found at the border between the pigment epithelium and the rod outer segment (Figs 3 and 5) They were located outside the cell bodies of the pigment epithelium In some cases they were associated with pigment epithelial processes but in other cases they seemed to be floating in the extracellular space

Phagosomes at later stages of degradation were seen within the pigment epithelial cells (Figs 4 and 5) but the early stages were lacking (Some of the structures might possibly represent lysosomes) The basal plasma membrane normally repeatedly folded was in most places fractured and destroyed (Fig 6)

Fig 4

The pigment epithelium (PE) shows a pycnotic nucleus (N) and a swollen cytoplasm with ruptured mitochondria (Mi) and endoplasmic tubules The phagosomes (Ph) are all at later stages of degradation At the upper left corner of the electron micrograph the swollen basement membrane (BM) is seen The rod outer segments (RO) do not show any significant signs of damage E endothelial cell of a choroidal capillary M melanin granule × 14 500


PE
N
Ph
NW
5

a fact that is probably of great importance in connection with the origin of the severe cell damage Also the basement membrane was changed It was partly swollen with aggregated internal structures (Figs 4 and 6) The continuous lining of the basement membrane seen in Fig ■ should not be mistaken for the basal plasma membrane of the pigment epithelial cell

The rod and cone outer segments did not differ significantly from their normal appearance (Figs 4 7 and 8) Membrane separations of the kind seen in Fig 4 may be found also in outer segment tips of normal preparations However the extracellular space between the outer segments was probably increase as compared to that of normal retina The rod and cone inner segments were perfectly normal in ultrastructure with well preserved mitochondria (Figs 7 and 8)

No damage was observed in the receptor nuclei and synaptic bodies (Fig 9) In the remaining part of the retina the Muller cells (Fig 9) the cell bodies of the inner nuclear layer and the processes of the outer and inner plexiform layers (Figs 9 and 10) showed some vacuoles and swollen mitochondria To a certain extent such changes were found also in the normal retina It seems however at least as to the Muller cells that their frequency of occurrence was slightly higher in sodium iodate treated preparations than in normal ones The ganglion cell axons (Fig 11) and cell bodies were undamaged

Discussion

The initial *c* wave oscillations with ■ frequency of about two per h are well demonstrated in earlier studies (Knave Persson Calissendorff & Nilsson 1973 Calissendorff Knave & Persson 1974 Skoog & Nilsson 1974)

Already at early stages (about two h) after sodium iodate injection the ultrastructure of the sheep pigment epithelium was drastically damaged whereas at the same time the neuroretina showed no or possibly very slight changes

These morphological findings are in good agreement with the electroretinographic results consisting of an immediate disappearance of the *c* wave (which

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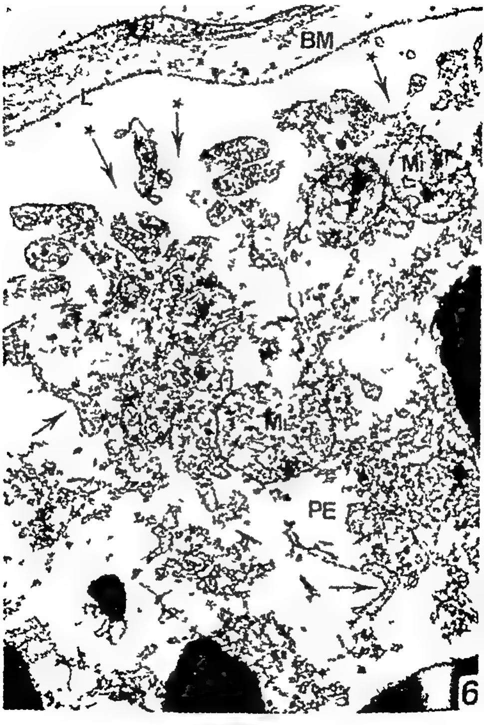
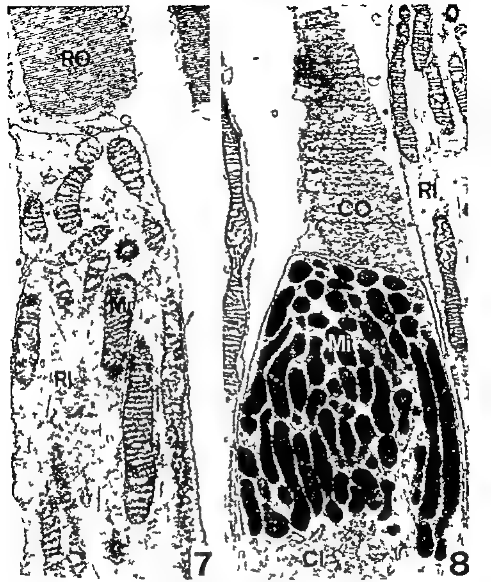
Fig 5

At this magnification the swollen appearance of the pigment epithelial cell (PE) is clearly demonstrated Arrows point at swollen tubules of the smooth surfaced endoplasmic reticulum Part of the pycnotic nucleus (N) ■ seen Membrane whirls (MW) are found outside the apical plasma membrane which is less distinct than normally Ph Phagosome at late stage of degradation or possibl a ly ornal structure × 31 000


BM
Mi
M
PE
6



Figs 7 and 8

The rod (RO) and cone (CO) outer segments look normal without signs of vesiculation of the disk membranes Also the rod (RI) and cone (CI) inner segments appear to be completely undamaged with well preserved mitochondria (Mi) × 27 000 and 14 000 resp

Fig 6

The distended basement membrane (BM) with its lining (L) is seen at the top of the figure The basal plasma membrane of the pigment epithelial cell (PE) is fractured (star labelled arrows) into pieces of which only remnants are seen The swollen cyto plasm shows distended tubules of the endoplasmic reticulum (arrows) as well as ruptured and completely disorganized mitochondria (Mi) × 43 000

Fig 9
The receptor nuclei (RN) and synaptic bodies (RS) seem to be unchanged A number of swollen mitochondria and vacuoles can be observed in the Muller cells (Mu) the dentrites (D) of the outer plexiform layer and the bipolar cell bodies (BC) × 9500

Figs 10 and 11

Some of the processes (Pr) of the inner plexiform layer contained vacuoles and swollen mitochondria The ganglion cell axons (Ax) did not show any signs of damage × 19 000 and 35 000 resp

was replaced by the negative azide insensitive potential (Noell 1953 1954) or the remnant negativity (Granit & Riddell 1934)) and a preservation of the *a* and *b* waves for about 80–100 min

As part of the "blood retina barrier" the plasma membranes of the pigment epithelial cells are known to have certain passive and active transport mechanisms (Steinberg & Miller 1973 Miller & Steinberg 1977a b) The severe damage to the plasma membranes particularly the basal plasma membrane of the pigment epithelial cells undoubtfully means that the permeability and the ion pump mechanisms of these membranes are dramatically changed The intracellular swelling including rupture of the mitochondria the endoplasmic reticulum and other cell organelles obviously is a result of the increase in permeability It seems very likely that the effects of sodium iodate on the membranes of the pigment epithelium start very rapidly The change in permeability ought to give rise also to a change in polarization of the pigment epithelial membranes Since the *c* wave of the ERG is generated when the apical (mainly) membrane of the pigment epithelium hyperpolarizes in response to a rod initiated decrease in external potassium during light stimulation (Steinberg Schmidt & Brown 1970 Schmidt & Steinberg 1971 Steinberg & Miller 1973 Oakley & Green 1976) it appears quite plausible that a change in permeability and in polarization of this kind would abolish the *c* wave

The preservation for some time of the *a* and *b* waves must imply that sodium iodate has no or at least no immediate toxic effect upon the neuroretina The decrease in these two potentials that occurs later could be caused either by a delayed direct effect of iodate on the neuroretina or more likely by an inability of the pigment epithelium to maintain its metabolic and barrier properties (See also Nilsson Knave & Persson 1977b) The morphological changes of the plasma membranes and the organelles of the pigment epithelial cells clearly imply that the metabolism of these cells is enormously disturbed Apparently at this stage the neuroretina was affected to an extent sufficient to give rise to a functional disturbance but not enough to cause morphological damage

Membrane whirls were seen extensively at the border between the pigment epithelium and the receptor tips This finding together with the observation that newly formed phagosomes were lacking within the pigment epithelial cells seem to mean that the latter cells have lost at least for the moment their ability to take part in the turnover process of the outer segments Normally the pigment epithelium engulfs detached packages of outer segment disks (Young & Bok 1969 Spitznas & Hogan 1970 Young 1971 Hogan Wood & Steinberg 1974 Steinberg Wood & Hogan 1977) However the lack of newly formed

phagosomes might at least partly be explained by the recent finding that the rods predominantly shed their disks at the onset of the light period (LaVail 1976 (rat) Basinger Hoffman & Matthes 1976 (frog)) and that shedding from cones occurs mainly at the beginning of the dark period (Young & O Day 19,7 (goldfish))

The rapid disappearance of the *c* wave and the delayed effect on the *a* and *b* waves observed in the present investigation is in agreement with the findings on the rabbit by Noell (1953 1954) except that in our case the *a* wave showed a decrease whereas Noell described a transient increase Suyama (1965) did not study the ERG until 24 h after the injection and thus did not describe the earliest changes However Suyama found that the disappearance of the *c* wave preceded that of the *a* and *b* waves

Grignolo Orzalesi & Calabria (1966) clearly showed in an electron micro scopic study of the sodium iodate injected rabbit that the ultrastructural damage of the pigment epithelium preceded that of the photoreceptors This is in agree ment with the observations of the present investigation Surprisingly enough Grignolo et al did not find any changes in the pigment epithelium until seven h after the injection Noell (1953 1954) found that the *c* wave was abo lished within a few minutes In the present study on the sheep the *c* wave was also abolished immediately and the morphological changes were most prominent already at two and a half hour after the injection of an equivalent dose of sodium iodate Grignolo et al did not perform electrophysiology

With respect to the morphology Noell (1953 1954) did not investigate the early changes His first sections were from day four after the injection At that time the pigment epithelium was almost completely destroyed but also the outer segments had degenerated to a great extent However Noell was of the opinion that the primary site of action of iodate was the pigment epithelium Suyama (1965) did not see any morphological changes until 48 h after the first injection of sodium iodate in the rabbit which is contradictory to the findings by Grignolo et al (1966) At that stage Suyama found numerous vacuoles in the pigment epithelium as well as in the receptor outer and inner segments The pigment epithelium was destroyed more quickly than the photoreceptors however

The present investigation on the sheep shows that sodium iodate rapidly and very severely affected the membrane properties and the cytoplasmic content of the pigment epithelium and that the morphological and electroretinographic changes in the neuroretina were delayed It thus seems that at a very early stage after injection of sodium iodate the preparation may be useful for the study of the effects on the neuroretina proper of drugs and other agents

References

Babel, J. (1970) The Retina. In: Bischoff, A., Ed. *Ultrastructure of the Peripheral Nervous System and Sense Organs*, pp. 339–441. G. Thieme Verlag, Stuttgart.

Basinger, S., Hoffman, R. & Matthes, M. (1976) Photoreceptor shedding is initiated by light in the frog retina. *Science 194*, 1074–1076.

Brown, K. T. & Watanabe, K. (1962) Isolation and identification of a receptor potential from the pure cone fovea of the monkey retina. *Nature (Lond.) 193*, 958–960.

Brown, K. T. & Wiesel, T. N. (1961a) Analysis of the intraretinal electroretinogram in the intact cat eye. *J. Physiol. (Lond.) 158*, 229–256.

Brown, K. T. & Wiesel, T. N. (1961b) Localization of origins of electroretinogram components by intraretinal recording in the intact cat eye. *J. Physiol. (Lond.) 158*, 257–280.

Calissendorff, B., Knave, B. & Persson, H. E. (1974) Cyclic variations in the c-wave amplitude of the sheep ERG. *Vision Res. 14*, 1141–1145.

Granit, R. (1974) *Sensory Mechanisms of the Retina*. Oxford University Press, London, New York and Toronto.

Granit, R. & Riddell, L. A. (1934) The electrical responses of light- and dark-adapted frogs' eyes to rhythmic and continuous stimuli. *J. Physiol. (Lond.) 81*, 1–28.

Grignolo, A., Orzalesi, N. & Calabria, G. A. (1966) Studies on the fine structure and the rhodopsin cycle of the rabbit retina in experimental degeneration induced by sodium iodate. *Exp. Eye Res. 5*, 86–97.

Hanitzsch, R. (1973) Intraretinal isolation of P III subcomponents in the isolated rabbit retina after treatment with sodium aspartate. *Vision Res. 13*, 2093–2102.

Hogan, M. J., Wood, I. & Steinberg, R. H. (1974) Phagocytosis by pigmented epithelium of human retinal cones. *Nature (Lond.) 252*, 305–307.

Knave, B., Moller, A. & Persson, H. E. (1972) A component analysis of the electroretinogram. *Vision Res. 12*, 1669–1684.

Knave, B., Persson, H. E., Calissendorff, B. & Nilsson, S. E. G. (1973) Selective effect of a new antituberculous drug 'rifampicin' on the c-wave of the sheep electroretinogram. *Acta ophthal. (Kbh.) 51*, 371–374.

Knave, B., Persson, H. E. & Nilsson, S. E. G. (1974) The effect of barbiturate on retinal functions. II. Effects on the c-wave of the electroretinogram and the standing potential of the sheep eye. *Acta physiol. scand. 91*, 180–186.

LaVail, M. M. (1976) Rod outer segment disk shedding in rat retina: relationship to cyclic lighting. *Science 194*, 1071–1074.

Lurie, M. (1973) *Aspects of interaction between retina and pigment epithelium: an electrophysiological study of the circulated frog eye*. Thesis, Mass. Inst. Techn.

Miller, R. F. & Dowling, J. E. (1970) Intracellular responses of the Müller (glial) cells of mudpuppy retina: their relation to the *b*-wave of the electroretinogram. *J. Neurophysiol. 33*, 323–341.

Miller, S. S. & Steinberg, R. H. (1977a) Passive ionic properties of frog retinal pigment epithelium. In preparation for publication.

Miller, S. S. & Steinberg, R. H. (1977b) Active transport of ions across frog retinal epithelium. In preparation for publication.

Murakami, M. & Kaneko, A. (1966) Differentiation of P III subcomponents in cold-blooded vertebrate retinas. *Vision Res. 6*, 627–636.

Nilsson S E G Knave B Lunt T & Persson H E (1975) The morphology of the sheep retina II The inner nuclear layer the ganglion cells and the plexiform layers *Acta ophthal (Kbh)* 51 612–627

Nilsson S E G Knave B & Persson H E (1977a) Changes in ultrastructure and function of the sheep pigment epithelium and retina induced by sodium iodate I The ultrastructure of the normal pigment epithelium of the sheep *Acta ophthal (Kbh)* 55 994–1006

Nilsson S E G Knave B & Persson H E (1977b) Changes in ultrastructure and function of the sheep pigment epithelium and retina induced by sodium iodate III Delayed effects *Acta ophthal (Kbh)* 55 1027–1043

Nilsson S E G Knave B Persson H E & Lunt T (1973) The morphology of the sheep retina I The receptor cells and the pigment epithelium *Acta ophthal (Kbh)* 51 599–611

Noell W K (1953) Studies on the electrophysiology and the metabolism of the retina *Project report U S Air Force SAM Project No 21-1201-0004* pp 1–222 Randolph Field Texas

Noell W K (1954) The origin of the electroretinogram *Amer J Ophthal 38* 78–93

Noell W K (1958) Differentiation metabolic organization and viability of the visual cell *Arch Ophthal (Chicago) 60* 702–733

Noell W K (1959) The visual cell electric and metabolic manifestations of its life processes *Amer J Ophthal 48* 347–370

Noell W K (1963) Cellular physiology of the retina *J opt Soc Amer* 53 36–48

Oakley II B & Green D G (1976) Correlation of light induced changes in retinal extracellular potassium concentration with *c* wave of the electroretinogram *J Neurophysiol* 39 1117–1133

Schmidt R & Steinberg R H (1971) Rod dependent intracellular responses to light recorded from the pigment epithelium of the cat retina *J Physiol (Lond)* 217 71–91

Skoog K O & Nilsson S E G (1974) The *c* wave of the human d c registered ERG II Cyclic variations of the *c* wave amplitude *Acta ophthal (Kbh)* 52 904–912

Spitznas M & Hogan M J (1970) Outer segments of photoreceptors and the retinal pigment epithelium *Arch Ophthal (Chicago) 84* 810–819

Steinberg R H (1969) Comparison of the intraretinal *b* wave and d c component in the area centralis of cat retina *Vision Res 9* 317–331

Steinberg R H & Miller S (1973) Aspects of electrolyte transport in frog pigment epithelium *Exp Eye Res 16* 365–372

Steinberg R H Schmidt R & Brown K T (1970) Intracellular responses to light from cat pigment epithelium origin of the electroretinogram *c* wave *Nature (Lond)* 227 728–730

Steinberg R H Wood I & Hogan M J (1977) Pigment epithelial ensheathment and phagocytosis of extrafoveal cones in human retina *Philosoph Trans R Soc Lond B* 277 459–474

Suyama T (1965) Electron microscopic study on experimental retinal degeneration induced by sodium iodate injection *Acta Soc ophthal jap 69* 440–460

Tomita T Murakami M & Pautler E L (1967) Spectral response curves of single cones in the carp *Vision Res 7* 519–531

Young R W (1971) Shedding of discs from rod outer segments in the rhesus monkey *J Ultrastruct Res 34* 190–203
Young R W & Bok D (1969) Participation of the retinal pigment epithelium in the rod outer segment renewal process *J Cell Biol 42* 392–403
Young R W & O Day W T (1977) Personal communication

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CHANGES IN ULTRASTRUCTURE AND FUNCTION OF THE SHEEP PIGMENT EPITHELIUM AND RETINA INDUCED BY SODIUM IODATE[1]

III Delayed Effects

BY

SVEN ERIK G NILSSON BENGT KNAVE and HANS E PERSSON

The delayed effects on the sheep pigment epithelium and retina of sodium iodate as studied three days after the injection included electrophysiological as well as morphological changes The *c* wave of the ERG was abolished and the *a* and *b* waves were substantially reduced in amplitude which was also the case as early as about 100–150 min after the injection The cornea negative potential earlier having replaced the *c* wave was no longer present however In addition to changes in the pigment epithelium seen already at an earlier stage marked ultrastructural damage was observed also in the neuroretina particularly in the photoreceptor cells and the Muller cells but involving all layers except the ganglion cell axons The receptor outer segments were greatly vesiculated and disorganized and the inner segments vacuolized The more vitread cells of the retina showed various degrees of oedema with distended mitochondria and a reduced amount of cytoplasmic structures It appears that the effects on the neuroretina of sodium iodate are to a great extent caused by the insufficient membrane and metabolic properties of the pigment epithelium

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From this series of three papers it can be concluded that sodium iodate primarily damaged the pigment epithelium thereby destroying the structural organization of the latter and abolishing the *c* wave Later the neuroretina was affected first in the form of *a* and *b* wave reductions and then also as ultrastructural changes It thus seems that the early stage after injection of sodium iodate may provide a valuable possibility of studying the electrophysiological effects on the neuroretina of various drugs without interference of the potentials from the pigment epithelium

Key words electron microscopy – electroretinography – *c wave* – *pigment* epithelium – retina – sodium iodate – toxicity – sheep

This series of three papers concerns I the normal ultrastructure of the sheep pigment epithelium (Nilsson Knave & Persson 1977a) II early electrophysiological and ultrastructural effects on the pigment epithelium and retina of sodium iodate (Nilsson Knave & Persson 1977b) and in the present paper III delayed effects of sodium iodate on the same structures

Noell (1953 1954) found strong electroretinographic evidence that sodium iodate damaged primarily the pigment epithelium and secondarily the retinal receptor cells The same sequential order of injury was observed in an ultrastructural study by Grignolo Orzalesi & Calabria (1966) Based on these findings sodium iodate has been used with the hope of selectively suppressing the

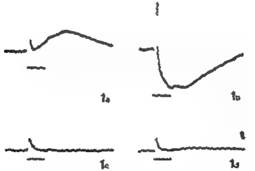


Fig 1

The d c recorded sheep ERG 1 a Normal control with *a* *b* and *c* waves 1 b Early stage (1 min) after sodium iodate injection The *c* wave is abolished and replaced by a cornea negative potential 1 c and d Later stage (5 days) after sodium iodate injection Markedly reduced *a* and *b* waves The *c* wave is abolished or can barely be seen The cornea negative potential has disappeared Stimulus duration 1 0 second Stimulus intensity about 5 log rel units above the *b* wave threshold Amplitude and time calibrations 100 µV and 1 0 second resp (Figs 1 a and 1 b represent data from the experiments concerning early stages (Nilsson Knave & Persson 1977b))

Fig 2

Survey of pigment epithelial cells (PE) and receptor outer and inner segments 3 days after sodium iodate injection Arrows defect in basement membrane RO rod outer segment CO cone outer segment RI rod inner segment V vesiculated rod outer segment disks x 6900


N
RO
PE
V
3

Figs 3 and 4

The cytoplasm of the pigment epithelial cells (PE) is largely changed into unidentifiable material Part of the chromatine is lost through the broken envelope of the nucleus (N) The apical and basal plasma membranes are no longer distinct in all places and the border between the pigment epithelial cells and the rod outer segments (RO) is rather diffuse Ph Phasosome in late degradation V vesiculated rod outer segment disks (Fig 3 is taken from the same area as Fig 2) × [illegible]200 and 18 500 resp

pigment epithelium in order to more or less isolate the effects on the neuro retinal responses of certain other agents (Noell 1953 1954 Knave Persson & Nilsson 1974) A model of this kind could be valuable also in connection with the study of other agents and drugs and perhaps more generally as a way of separating pigment epithelial and neuroretinal activities In such a case one would need a thorough knowledge of the different phases of the toxicity exerted by sodium iodate which can best be achieved by correlating electrophysiology and ultrastructure in the same experiment Earlier studies on the subject (Noell

1953, 1954, 1963; Grignolo, Orzalesi & Calabria 1966; Suyama 1965; Babel 1970), some of them very extensive, either do not include morphology of the early stages or do not correlate ultrastructural findings with electrophysiology, however. For this reason the present investigation was undertaken.

Material and Methods

Two successful experiments performed on the dark adapted sheep eye *in situ* provide the basis for the results of this study.

30 mg sodium iodate/kg b. wt. was injected i.v. through a foreleg vein of the sheep. Three days later the d. c. recorded ERG was followed for 56 min according to a method summarized in the second paper of this series (Nilsson, Knave & Persson 1977b) and described in detail earlier (Knave, Møller & Persson 1972). The stimulus intensity was about 5 log relative units above the *b* wave threshold, the stimulus duration 1.0 second and the stimulus interval 2 min. Two responses were summated.

As soon as the ERG recordings were completed, the eyes were fixed by perfusion via the common carotid arteries and prepared for electron microscopy according to the method described in the first paper of this series (Nilsson, Knave & Persson 1977a).

Observations

Electrophysiology

The average amplitudes of the *a* and *b* waves of the ERG three days after the injection of sodium iodate were about 10 μV and 170 μV, respectively (Figs. 1 c and 1 d). This means a pronounced reduction as compared to the untreated sheep (Fig. 1 a). The *c* wave was abolished (Fig. 1 c) or could in some cases be traced as a deflection of a few microvolts (Fig. 1 d). The cornea negative potential replacing the *c* wave at the early stage after sodium injection (Fig. 1 b) was no longer present.

Ultrastructure

The ultrastructural changes of the pigment epithelial cells at this later stage (Figs. 2–4) were in most respects similar to or somewhat more pronounced than those described in the preceding paper (Nilsson, Knave & Persson 1977b) concerning an earlier stage (about 2 h) after sodium iodate injection. A striking difference between the two stages, however, was the severe damage also of the neuroretina (Figs. 2–10), particularly the photoreceptors (Figs. 2–7), seen at this later stage.

Fig 5
Macrophage like pigment epithelial cell (Ma) containing numerous phagosomes (Ph) V vesiculated rod outer segment disks RI rod inner segments × 8400

Defects sometimes extensive were observed in the endothelium of the cho roidal capillaries and in the basement membrane (Fig 2) In many places the basal as well as the apical plasma membrane of the pigment epithelial cells were broken Often no distinct border could be identified between the pigment epithelium and the rod outer segments (Figs 3–4)

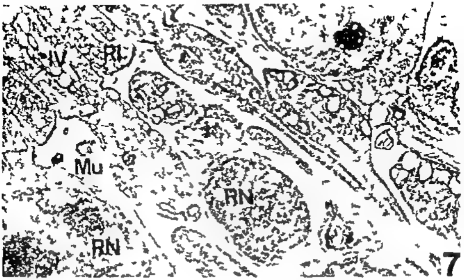
In the pigment epithelial cell the nuclear envelope was often broken and in some cases large portions of the chromatine was lost (Figs 2–3) The cytoplasm was changed to a great extent into an amorfous mass of unidentifiable material frequently with large empty spaces (Figs 2–4) No new phagosomes were seen

Fig 6

Receptor damage in the form of distorted cone outer segment disks (CO) and rod inner segment vacuolization (IV) is demonstrated (Taken from the same area as in Fig 2) ×15 300

Figs 7 and 8

Electron micrographs of the retina at the level of the receptor inner segments (PI) and nuclei (RN) Whereas vacuoles (IV) are seen in the inner segments the nuclei are well preserved At this level the Muller cells (Mu) are very swollen and devoid of internal structures What seems to be a migrating pigmented cell (MP) is seen among the receptor inner segments and nuclei This cell is very distended It contains what appears to be outer segment material ×8500


IV
RL
Mu
RN
RN
7

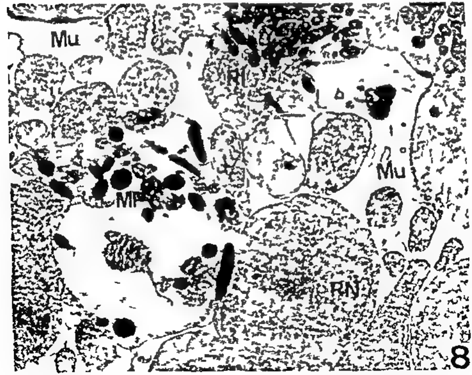

Mu
RL
Mu
MP
RN
8

Fig 9

The receptor synaptic bodies (RS) appear to be normal The Muller cells (Mu) are swollen The bipolar cells (BC) and the dendrites (D) of the outer plexiform layer show markedly damaged mitochondria Ca Capillary × 10 700

Fig 10
Many neuronal processes (Pr) of the inner plexiform layer are swollen and lack cytoplasmic structures At this level the Muller cells (Mu) are not markedly damaged *The ganglion cell axons (Ax) do not show any obvious signs of injury* × *8700*

but structures resembling older phagosomes were present (Fig 4) Mitochondria and tubules of the endoplasmic reticulum were not recognized (Figs 3–4)

A limitated number of a different kind of pigmented cells were found among the injured pigment epithelial cells They were much bigger than regular pigment epithelial cells and protruded into the visual cell layer They showed a large number of phagosomes most of them containing membranes similar to outer segment material (Fig 5) In some cases also melanin pigment granules were seen within phagosomes Since the membraneous material in many cases was not highly degradated the majority of the phagosomes appeared to be rather newly formed

Occasionally also cells that seem to be migrating pigmented cells could be observed among the receptor inner segments and nuclei as in Fig 8 In this case the pigmented cell was very swollen It contained membrane packages presumably originating in the visual cells

The photoreceptor outer segments showed signs of heavy damage in the form of vesiculation and distortion of the membrane disks (Figs 2–6) It was often observed that certain parts of an outer segment had a normal appearance whereas other parts of the same outer segment were vesiculated

In most photoreceptor inner segments vacuoles of different sizes were seen (Figs 2 5–7) The mitochondria were generally fairly well preserved however The receptor nuclei (Figs 7–9) and synaptic bodies (Fig 9) did not show any obvious signs of toxic influence

The distal parts of the Muller cells located among the receptor cells in the outer plexiform layer and in the nuclear layer were markedly swollen and devoid of cytoplasmic structures In the micrographs they are seen as more or less empty profiles (Figs 7–9) As to the more proximal parts of the Muller cells the damage was much less pronounced (Fig 10)

In the dendrites of the outer plexiform layer the cell bodies of the inner nuclear layer (Fig 9) the processes of the inner plexiform layer (Fig 10) as well as in many ganglion cells the mitochondria were very distended and lacking cristae Many profiles of the processes of the inner plexiform layer showed a more prominent oedema and they were to a great extent devoid of internal structures (Fig 10) The ganglion cell axons were rather well preserved (Fig 10)

Discussion

The earliest effects of sodium iodate on the sheep pigment epithelium and retina were limited to ultrastructural damage of the pigment epithelial cells concomitant with abolishment of the *c* wave which was replaced by a cornea

negative potential The neuroretina was left ultrastructurally intact and the *a* and *b* waves were preserved for about 80–100 min (Nilsson Knave & Persson 1977b) The present investigation of the later changes showed pronounced morphological changes also in the neuroretina particularly in the photoreceptors and in addition to the abolished *c* wave also markedly reduced *a* and *b* waves These findings fit well with the knowledge that the *c* wave is generated mainly in the pigment epithelium as a rod initiated response upon light stimulation (Steinberg Schmidt & Brown 1970 Schmidt & Steinberg 1971 Steinberg & Miller 1973 Oakley & Green 1976) and that the *a* wave (Brown & Watanabe 1962 Murakami & Kaneko 1966 Tomita Murakami & Pautler 1967) and the *b* wave (Brown & Wiesel 1961a b Steinberg 1969 Miller & Dowling 1970) originate in the neuroretina

Since the photoreceptors are dependent upon the metabolism of the pigment epithelium it is evident that the receptors cannot remain undamaged in the long run when the pigment epithelial cells are heavily injured in the form of greatly disturbed plasma membrane permeability and transport properties and destroyed cytoplasmic structures (The pigment epithelial damage was shown more extensively in the preceding paper (Nilsson Knave & Persson 1977b)) It is not possible to decide whether the changes in the neuroretina are caused by a direct toxicity of sodium iodate by the insufficiency of the pigment epithelium or by both factors The delayed effect speaks in favour of the pigment epithelial insufficiency as being the main reason however

Whereas in the present study as well as in the paper by Grignolo Orzalesi & Calabria (1966) (rabbit) the morphological damage of the pigment epithelium clearly preceded that of the photoreceptor outer segments Suyama (1965) (rabbit) found that the changes appeared simultaneously in both layers and not until 48 h after the injection Suyama observed however that as the injury proceeded the pigment epithelial cells were destroyed earlier than the visual cells Noell (1953 1954) (rabbit) did not perform light microscopy until 4 days after the injection and at that time the pigment epithelial cells and the outer segments were both markedly damaged particularly the former ones Noell was of the opinion that the primary site of action of iodate was the pigment epithelium

In our material not only the outer segments but also the inner segments were undoubtedly changed Grignolo et al (1966) found no ultrastructural alterations in the *inner segment* in the rabbit whereas Suyama (1965) and Babel (1970) described such damage Since Grignolo et al and Suyama used the same dosage and the same species the difference must have a background other than a species difference In light microscopy Noell (1953 1954) observed very little or no inner segment involvement

Retinal oedema is seen ophthalmoscopically after sodium iodate injection (Noell 1953 Suyama 1965 Babel 1970) The marked swelling and destruction of the Muller cells particularly of their distal parts found in the present study by Grignolo et al (1966) and by Babel (1970) represents one of the ultra structural signs of this oedema

Noell (1953) concluded from his light microscopical investigation that the layers vitread to the external limiting membrane were relatively well preserved The ultrastructural studies by Grignolo et al (1966) Suyama (1965) and Babel (1970) do not describe the layers proximal to the visual cells In the present investigation marked changes were seen in the entire retina except for the layer of the ganglion cell axons They were most pronounced in the photo receptors however The changes in the proximal parts of the retina are well consistent with retinal oedema

In the layer of heavily damaged pigment epithelial cell also a different kind of pigmented cells were observed These cells were much bigger than the re gular ones and showed a large number of phagosomes containing outer segment material melanin granules etc They were described also by Grignolo et al (1966) and are regarded as pigment epithelial cells that survived and dedifferentiated into macrophages which take care of the debris from destroyed pig ment epithelial and photoreceptor cells In addition the present investigation showed pigmented cells located also among the photoreceptor nuclei These cells appeared to be migrating macrophages It seems that this is the same kind of transformation of pigment epithelial cells that was described in elegant experiments concerning retinal detachment by Machemer & Laqua (1975) Mandelcorn Machemer Fineberg & Hersch (1975) and by Mueller Jensen Machemer & Azarnia (1975) On the other hand it cannot be fully excluded that the cell containing engulfed material in Fig 8 is a Muller cell

Grignolo et al (1966) studied the repairing process further and found that the modified pigment epithelial cells increased in number and later covered the basement membrane Since the receptor outer segments were lost a space separated these modified cells from the inner segments

At the early stage after sodium iodate injection the *c* wave was abolished and replaced by a cornea negative potential This is in agreement with the observations by Noell (1953 1954) However Suyama s recordings at 24 h after the injection do not show the cornea negative potential (1965) It is evident that the *c* wave which is a rod initiated response generated mainly across the apical membrane of the pigment epithelial cells upon light stimulation cannot be elicited when the plasma membranes (particularly the basal one) are more or less destroyed A destruction of both membranes must cause a depolarization

of the cell Three days after the injection we found that the cornea negative potential initially replacing the c wave had disappeared

Noell (1953 1954) does not discuss as far as we can see what happens to this cornea negative (and azide insensitive) potential in long term experiments However he observed that iodoacetic acid which is considered to destroy the visual cells also abolished the cornea negative potential Noell thus concludes that the latter potential may be generated by the visual cells It seems difficult to establish the exact origin of this potential It shows similarities to slow P III a slow negative potential (Granit 1947) with at least two subcomponents from the distal parts of the receptors and from the inner nuclear layer respectively (Murakami & Kaneko 1966 Hanitzsch 1973) It cannot be excluded that also the Muller cells might be involved in the generation of slow P III In any case the cornea negative potential disappeared with the damage to the neuroretina exceeded a certain limit

In our previous paper (Nilsson Knave & Persson 1977b) it was shown that the *a* and *b* waves decreased in amplitude about 80–100 min after the injection of iodate The decrease was studied for another 25–50 min Thereafter we did not examine the ERG until three days after the injection of iodate and at that stage the *a* and *b* waves were still very small Noell (1953 1954) found that the *a* wave increased after two to six h decreased after one day and disappeared almost completely on the fifth day The *b* wave was reduced after two to six h increased after one day and again reduced after the fourth day It disappeared or was minimal between day 8 and 14 We did not see an increase of the *a* wave in our experiments but such changes apparently are time dependent and also dose dependent since Noell observed that larger doses of iodate gave rise to a permanent decrease of the *b* wave about one h after the injection In Suyama s experiments the *a* and *b* waves disappeared 72 h after the injection (1965) The *c* wave was abolished earlier Babel (1970) states that the ERG could be extinguished as early as six h after the injection (larger doses than the other investigators) He did not discuss the different waves of the ERG but the statement probably concerned the *a* and *b* waves

The fact that in the present investigation a reduction in *a* and *b* wave amplitudes was observed prior to ultrastructural changes in the neuroretina shows that a functional impairment may very well precede a morphological one

In conclusion it can be said that sodium iodate caused damage primarily to the pigment epithelium and thereby abolished the *c* wave of the ERG Later the neuroretina particularly the photoreceptor layer was affected probably as a result mainly of insufficient metabolic functions and membrane properties of the pigment epithelium The *a* and *b* waves decreased prior to the appearance of ultrastructural damage in the neuroretina It seems that during an early

stage after iodate injection the activity of the pigment epithelium is destroyed whereas the function of the neuroretina is still preserved and that such a stage could be useful for a closer analysis of the neuroretinal responses e g concerning the effects of various drugs

References

Babel J (1970) The retina In Bischoff A Ed *Ultrastructure of the Peripheral Nervous System and Sense Organs* pp 339–441 G Thieme Verlag Stuttgart

Brown K T & Watanabe K (1962) Isolation and identification of a receptor potential from the pure cone fovea of the monkey retina *Nature (Lond) 193* 958–960

Brown K T & Wiesel T N (1961a) Analysis of the intraretinal electroretinogram in the intact cat eye *J Physiol (Lond) 158* 229–256

Brown K T & Wiesel T N (1961b) Localization of origins of electroretinogram components by intraretinal recording in the intact cat eye *J Physiol (Lond) 158* 257–280

Granit R (1947) *Sensory Mechanisms of the Retina* Oxford University Press London New York and Toronto

Grignolo A Orzalesi N & Calabria G A (1966) Studies on the fine structure and the rhodopsin cycle of the rabbit retina in experimental degeneration induced by sodium iodate *Exp Eye Res 5* 86–97

Hanitzsch R (1973) Intraretinal isolation of P III subcomponents in the isolated rabbit retina after treatment with sodium aspartate *Vision Res 13* 2093–2102

Knave B Moller A & Persson H E (1972) A component analysis of the electroretinogram *Vision Res 21* 1669–1684

Knave B Persson H E & Nilsson S E G (1974) The effect of barbiturate on retinal functions II Effects on the *c* wave of the electroretinogram and the standing potential of the sheep eye *Acta physiol scand 91* 180–186

Machemer R & Laqua H (1975) Pigment epithelium proliferation in retinal detachment (Massive preretinal proliferation) *Amer J Ophthal 80* 1–23

Mandelcorn M S Machemer R Fineberg E & Hersch S B (1975) Proliferation and metaplasia of intravitreal retinal pigment epithelium cell autotransplants *Amer J Ophthal 80* 227–237

Miller R F & Dowling J E (1970) Intracellular responses of the Muller (glial) cells of mudpuppy retina their relation to the *b* wave of the electroretinogram *J Neurophysiol 33* 323–341

Mueller Jensen K Machemer R & Azarnia R (1975) Autotransplantation of retinal pigment epithelium in intravitreal diffusion chamber *Amer J Ophthal 80* 530–537

Murakami M & Kaneko A (1966) Differentiation of P III subcomponents in cold blooded vertebrate retinas *Vision Res 6* 627–636

Nilsson S E G Knave B & Persson H E (1977a) Changes in ultrastructure and function of the sheep pigment epithelium and retina induced by sodium iodate I The ultrastructure of the normal pigment epithelium of the sheep *Acta ophthal (Kbh) 55* 994–1006

Nilsson S E G Knave B & Persson H E (1977b) Changes in ultrastructure and function of the sheep pigment epithelium and retina induced by sodium iodate II Early effects *Acta ophthal (Kbh)* 55 1007–1026

Noell W K (1953) Studies on the electrophysiology and the metabolism of the retina *Project report U S Air Force SAM Project No 21–1201–0004* pp 1–122 Randolph Field Texas

Noell W K (1954) The origin of the electroretinogram *Amer J Ophthal* 38 78–93

Noell W K (1963) Cellular physiology of the retina *J opt Soc Amer* 53 36–48

Oakley II B & Green D G (1976) Correlation of light induced changes in retinal extracellular potassium concentration with the *c* wave of the electroretinogram *J Neurophysiol* 39 111 –1133

Schmidt R & Steinberg R H (1971) Rod dependent intracellular responses to light recorded from the pigment epithelium of the cat retina *J Physiol (Lond)* 217 71–91

Steinberg R H (1969) Comparison of the intraretinal *b* wave and d c component in the area centralis of cat retina *Vision Res* 9 317–331

Steinberg R H & Miller S (1973) Aspects of electrolyte transport in frog pigment epithelium *Exp Eye Res* 16 365–372

Steinberg R H Schmidt R & Brown K T (1970) Intracellular responses to light from cat pigment epithelium origin of the electroretinogram *c* wave *Nature (Lond)* 227 728–730

Suyama T (1965) Electron microscopic study on experimental retinal degeneration induced by sodium iodate injection *Acta Soc ophthal jap* 69 440–460

Tomita T Murakami M & Pautler E L (1967) Spectral response curves of single cones in the carp *Vision Res* 7 519–531

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L Koornneef Spatial aspects of orbital musculo fibrous tissues in man A new anatomical and histological approach Swets & Zeitlinger Amsterdam 1977 pp 165 Price Dutch Guilders 67 60

This monograph is a thesis from the Netherlands Ophthalmic Research Institute, Amsterdam

A three dimensional anatomical description of orbital topography is presented using a new technique whereby the relationship between the orbital wall the orbital connective tissue and the orbital fat is demonstrated using thick transparent slides of microscopic and submacroscopic structures This new analysis of the orbital connective tissue system suggests that the adipose tissue and the connective tissue septra might play a more important role for eye movements than previously assumed The specific spatial architecture of the orbital septra is visualized in an appendix with 12 stereoscopic anaglyphs The book is primarily intended for those ophthalmologists who are especially interested in orbital and eye muscle surgery

K Norskov

Computerized Tomography The international journal of radiological diagnosis using CT scanners Vol 1 No 1 Pergamon Press 1977

The subspecialization of medicine still gives birth to new periodicals This makes it increasingly difficult for the MD to keep pace in all directions – due to lack of time (and of money too) It reflects however a real need especially in the newly invented more technical branches including computerized tomography (CT of brain as well as of whole body) Indeed this is the indispensable roentgenological scoop of the 70 ies and the existing periodicals have not been able to cope with the rapidly expanding needs of CT scan authors This new journal will therefore be warmly welcomed by CT consumers

A whole body journal however gives an unfavourable cost benefit ratio for the clinical *ophthalmologist* whose problems will be dealt with on only a low percentage of the pages in number 1 thus 5 % (6/130 pages) It is therefore to be hoped that the orbital CT highlights will still be issued in the existing clinical journals (also)

The new journal will appear quarterly There is a special price of 30$ a year for individual subscribers who will certify that the journal is for their personal use only

H Fledelius